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FILE 'EMBASE' ENTERED AT 11:54:29 ON 11 SEP 2002
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 FILE COVERS 1974 TO 5 Sep 2002 (20020905/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> e neonate/ct
E#   FREQUENCY    AT      TERM
--   ---------    --      ----
E1           0     2      NEONATAL UNDERWEIGHT/CT
E2           0     2      NEONATAL WEIGHT/CT
E3           0     2  --> NEONATE/CT
E4           0     2      NEONATE ASPHYXIA/CT
E5           0     2      NEONATE DEATH/CT
E6           0     2      NEONATE HEMOLYTIC DISEASE/CT
E7           0     2      NEONATE JAUNDICE/CT
E8           0     2      NEONATE,PREMATURE/CT
E9           5            NEONATICIDE/CT
E10        500     7      NEONATOLOGY/CT
E11          0     2      NEONATUS/CT
E12          0     2      NEONATUS DISEASE/CT

=> e e3+all
E1           0    -->    neonate/CT
E2      154802    USE    newborn/CT
*********  END***

=> s e2
L12      154802 NEWBORN/CT

=> file caplus embase uspatfull
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     1.11      72.74

FILE 'CAPLUS' ENTERED AT 11:55:08 ON 11 SEP 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE 'EMBASE' ENTERED AT 11:55:08 ON 11 SEP 2002
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FILE 'USPATFULL' ENTERED AT 11:55:08 ON 11 SEP 2002
CA INDEXING COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

=> d his

     (FILE 'HOME' ENTERED AT 11:48:03 ON 11 SEP 2002)

     FILE 'EMBASE' ENTERED AT 11:48:16 ON 11 SEP 2002
                E NECROTIZING ENTEROCOLITIS/CT
                E E3 + ALL
L1         163885 S E1-E12
                E NECROTIZ? ENTEROCOLITIS/CT
                E NECROTIZING ENTEROCOLITIS/CT
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L2          1123 S E3-E15
L3        163885 S L1 OR L2
L4             0 S TNF/CT
L5             0 S TUMOR NECROTIZING FACTOR/CT

     FILE 'REGISTRY' ENTERED AT 11:51:02 ON 11 SEP 2002
L6             5 S TNF/CN
L7             1 S 308079-78-9/RN

     FILE 'EMBASE, CAPLUS, USPATFULL' ENTERED AT 11:52:18 ON 11 SEP 2002
L8        164711 S L3 OR (NECROTIZ#### (5W) ENTEROCOL##########)
L9        123958 S L7 OR TNF OR (TUMOR NECROSIS FACTOR#)
L10         2092 S L8 (10W) L9
L11         2092 S L8 AND L9

     FILE 'EMBASE' ENTERED AT 11:54:29 ON 11 SEP 2002
                E NEONATE/CT
                E E3+ALL
L12       154802 S E2

     FILE 'CAPLUS, EMBASE, USPATFULL' ENTERED AT 11:55:08 ON 11 SEP 2002

=> s l12 or neonate# or newborn# or (new born)
L13      262393 L12 OR NEONATE# OR NEWBORN# OR (NEW BORN)

=> s l13 and l11
L14           55 L13 AND L11

=> duplicate remove l14
DUPLICATE PREFERENCE IS 'CAPLUS, EMBASE, USPATFULL'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L14
L15           50 DUPLICATE REMOVE L14 (5 DUPLICATES REMOVED)

=> d 1-50 ab ibib kwic

L15  ANSWER 1 OF 50  USPATFULL
AB     The present invention relates to novel proteins. More specifically,
       isolated nucleic acid molecules are provided encoding novel
       polypeptides. Novel polypeptides and antibodies that bind to these
       polypeptides are provided. Also provided are vectors, host cells, and
       recombinant and synthetic methods for producing human polynucleotides
       and/or polypeptides, and antibodies. The invention further relates to
       diagnostic and therapeutic methods useful for diagnosing, treating,
       preventing and/or prognosing disorders related to these novel
       polypeptides. The invention further relates to screening methods for
       identifying agonists and antagonists of polynucleotides and
polypeptides
       of the invention. The present invention further relates to methods
       and/or compositions for inhibiting or enhancing the production and
       function of the polypeptides of the present invention.

       The present invention relates to novel proteins. More specifically,
       isolated nucleic acid molecules are provided encoding novel
       polypeptides. Novel polypeptides and antibodies that bind to these
       polypeptides are provided. Also provided are vectors, host cells, and
       recombinant and synthetic methods for producing human polynucleotides
       and/or polypeptides, and antibodies. The invention further relates to
       diagnostic and therapeutic methods useful for diagnosing, treating,
       preventing and/or prognosing disorders related to these novel
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polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

ACCESSION NUMBER: 2002:164712 USPATFULL
TITLE: Nucleic acids, proteins, and antibodies
INVENTOR(S): Rosen, Craig A., Laytonsville, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Barash, Steven C., Rockville, MD, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002086330	A1	20020704	
APPLICATION INFO.:	US 2001-764893	A1	20010117	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-179065P	20000131	(60)
	US 2000-180628P	20000204	(60)
	US 2000-214886P	20000628	(60)
	US 2000-217487P	20000711	(60)
	US 2000-225758P	20000814	(60)
	US 2000-220963P	20000726	(60)
	US 2000-217496P	20000711	(60)
	US 2000-225447P	20000814	(60)
	US 2000-218290P	20000714	(60)
	US 2000-225757P	20000814	(60)
	US 2000-226868P	20000822	(60)
	US 2000-216647P	20000707	(60)
	US 2000-225267P	20000814	(60)
	US 2000-216880P	20000707	(60)
	US 2000-225270P	20000814	(60)
	US 2000-251869P	20001208	(60)
	US 2000-235834P	20000927	(60)
	US 2000-234274P	20000921	(60)
	US 2000-234223P	20000921	(60)
	US 2000-228924P	20000830	(60)
	US 2000-224518P	20000814	(60)
	US 2000-236369P	20000929	(60)
	US 2000-224519P	20000814	(60)
	US 2000-220964P	20000726	(60)
	US 2000-241809P	20001020	(60)
	US 2000-249299P	20001117	(60)
	US 2000-236327P	20000929	(60)
	US 2000-241785P	20001020	(60)
	US 2000-244617P	20001101	(60)
	US 2000-225268P	20000814	(60)
	US 2000-236368P	20000929	(60)
	US 2000-251856P	20001208	(60)
	US 2000-251868P	20001208	(60)
	US 2000-229344P	20000901	(60)
	US 2000-234997P	20000925	(60)
	US 2000-229343P	20000901	(60)
	US 2000-229345P	20000901	(60)
	US 2000-229287P	20000901	(60)
	US 2000-229513P	20000905	(60)
	US 2000-231413P	20000908	(60)
	US 2000-229509P	20000905	(60)

	US 2000-236367P	20000929 (60)
	US 2000-237039P	20001002 (60)
	US 2000-237038P	20001002 (60)
	US 2000-236370P	20000929 (60)
	US 2000-236802P	20001002 (60)
	US 2000-237037P	20001002 (60)
	US 2000-237040P	20001002 (60)
	US 2000-240960P	20001020 (60)
	US 2000-239935P	20001013 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850	
NUMBER OF CLAIMS:	24	
EXEMPLARY CLAIM:	1	
LINE COUNT:	25862	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . neonatal respiratory distress syndrome decreases markedly after 36 weeks of gestation. Likewise, the incidence of neonatal patent ductus arteriosus and **necrotizing enterocolitis** decreases markedly after 32 weeks of gestation, and high grade intraventricular hemorrhage diminishes rapidly after 27 weeks and is virtually. . .

SUMM . . . line

H0288	Human OB HOS control fraction I XR	Human Osteoblastoma HOS cell line	Bone	Cell Line Uni-ZAP
H0294	Amniotic Cells - **TNF** induced XR	Amniotic Cells - **TNF** induced	Placenta	Cell Line Uni-ZAP
H0295	Amniotic Cells - Primary Culture XR	Amniotic Cells - Primary Culture	Placenta	Cell Line Uni-ZAP
H0305	CD34 positive cells. . .			
SUMM	. . . Uni-ZAP			
	cortex, epileptic; re-excision XR	Cortex, Epileptic		
S0228	PSMIX PCRII	PBLS, 7TM receptor enriched		
S0242	Synovial Fibroblasts pSport 1	Synovial Fibroblasts		
	(III/**TNF**), subt			
S0250	Human Osteoblasts II disease pCMVSport 2.0	Human Osteoblasts	Femur	
S0252	7TM-PIMIX PCRII	PBLS, 7TM receptor enriched		
S0260	Spinal Cord, re-	Spinal. . .		

SUMM . . . may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as **tumor necrosis factor**, a-interferon, .beta.-interferon, nerve growth factor, platelet derived growth factor,

tissue plasminogen activator, an apoptotic agent, e.g., **TNF** -alpha, **TNF**-beta, AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi et. . .

SUMM . . . a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble **TNF** receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the. . .

SUMM . . . complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (e.g., **TNF** or IL-1.), respiratory disorders (e.g., asthma and allergy); gastrointestinal disorders (e.g., inflammatory bowel disease); cancers (e.g., gastric, ovarian, lung, bladder,. . .

SUMM . . . and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among aged populations and/or **neonates**.

SUMM . . . indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as **tumor necrosis factor (TNF)** receptor-1, CD95 (Fas/APO-1), **TNF**-receptor-related apoptosis-mediated protein (TRAMP) and **TNF**-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by. . .

DETD . . . Week Old Early Stage Human, II Uni-ZAP XR LP04

HE2Q

HPTS HPTT HPTU Human Pituitary, subtracted
Uni-ZAP XR LP04

HAUA HAUB HAUC Amniotic Cells-**TNF** induced
Uni-ZAP XR LP04

HAQA HAQB HAQC HAQD Amniotic Cells-Primary Culture
Uni-ZAP XR LP04

HWTA HWTB HWTC wilm's tumor
Uni-ZAP XR LP04

HBSD. . . Jurkat T-cell G1 phase pBS
LP05

HJBA HJBB HJBC HJBD Jurkat T-Cell, S phase
pBS LP05

HAFA HAFB Aorta endothelial cells + **TNF**-a
pBS LP05

HAWA HAWB HAWC Human White Adipose
pBS LP05

HTNA HTNB Human Thyroid
pBS LP05

HONA Normal Ovary, Premenopausal
pBS LP05

HARA HARB. . .

DETD . . . 1 LP10

HFIA HFIB HFIC Synovial Fibroblasts (control)
pSport 1 LP10

HFIH HFII HFIJ Synovial hypoxia
pSport 1 LP10

HFIT HFIU HFIV Synovial IL-1/**TNF** stimulated
pSport 1 LP10

HGCA Messangial cell, frac 1
pSport1 LP10

HMVA HMVB HMVC Bone Marrow Stromal Cell, untreated
pSport1 LP10
HFIX HFIY HFIZ Synovial Fibroblasts (I11/**TNF**),
subt pSport1 LP10
HFOX HFOY HFOZ Synovial hypoxia-RSF subtracted
pSport1 LP10
HMQA HMQB HMQC HMQD Human Activated Monocytes
Uni-ZAP XR LP11
HLIA HLIB. . . Uni-ZAP XR LP013
HOQB Human OB HOS treated (1 nM E2)
Uni-ZAP XR LP013
fraction I
HAUA HAUB HAUC Amniotic Cells - **TNF** induced
Uni-ZAP XR LP013
HAQA HAQB HAQC HAQD Amniotic Cells - Primary Culture
Uni-ZAP XR LP013
HROA HROC HUMAN STOMACH
Uni-ZAP XR. . . HPIC LNCAP prostate cell line
Uni-ZAP XR LP013
HPJA HPJB HPJC PC3 Prostate cell line
Uni-ZAP XR LP013
HBTA Bone Marrow Stroma, **TNF** & LPS
ind Uni-ZAP XR LP013
HMCF HMCG HMCH HMCI HMCJ Macrophage-oxLDL; re-excision
Uni-ZAP XR LP013
HAGG HAGH HAGI Human Amygdala; re-excision. . .

DETD . . . antibodies Q4120 and RPAT4, the anti-CCR3 antibody 7B11, the anti-gp120 antibodies 17b, 48d, 447-52D, 257-D, 268D and 50.1, anti-Tat antibodies, anti-**TNF**-.alpha. antibodies, and monoclonal antibody 33A; aryl hydrocarbon (AH) receptor agonists and antagonists such as TCDD, 3,3',4,4',5-pentachlorobiphenyl, 3,3',4,4'-tetrachlorobiphenyl, and .alpha.-naphthoflavone (WO. . .

DETD . . . fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, **tumor necrosis factor** alpha, hepatocyte growth factor, insulin-like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric. . .

DETD . . . include, but are not limited to, IL2, IL3, IL4, IL5, IL6, L7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and **TNF**-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta,. . .

DETD [0959] In one embodiment, the Therapeutics of the invention are administered in combination with members of the **TNF** family. **TNF**, **TNF**-related or **TNF**-like molecules that may be administered with the Therapeutics of the invention include, but are not limited to, soluble forms of **TNF**-alpha, lymphotoxin-alpha (LT-alpha, also known as **TNF**-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, **TNF**-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), OPG, and neutrokine-alpha. . .

DETD [1020] One of the best studied classes of B-cell co-stimulatory proteins is the **TNF**-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands CD154, CD70, and CD153 have been found to. . .

DETD . . . of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as **TNF**-.alpha., causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation. . .

DETD . . . or other stimuli. Their death results from internally regulated processes (apoptosis). Addition to the culture of activating factors, such as **TNF**-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml **TNF**-alpha (negative control), and in the presence of varying concentrations of the compound to be tested. Cells are suspended at a. . .

DETD . . . LPS (10 ng/ml) is then added. Conditioned media are collected after 24 h and kept frozen until use. Measurement of **TNF** -alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e.g., R & D Systems (Minneapolis, Minn.)). . .

DETD Suppression of **TNF** Alpha-induced Adhesion Molecule Expression by an Agonist or Antagonist of the Invention

DETD [1097] **Tumor necrosis factor** alpha (**TNF**-a), a potent proinflamnmatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a. . .

DETD [1098] The potential of an agonist or antagonist of the invention to mediate a suppression of **TNF**-a induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on **TNF**-a treated ECs when co-stimulated with a member of the FGF family of proteins.

DETD . . . (Nuclear Factor KB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines TL-1 and **TNF**, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products.. . .

DETD . . . method for assaying supematants with these stable Jurkat T-cells is also described in Example 32. As a positive control, exogenous **TNF** alpha (0.1,1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

DETD . . . M-1985, M-2225, M-2105, M-2110, and M-2255. The first four are MMP substrates and the last one is a substrate of **tumor necrosis factor**-.alpha. (**TNF**-.alpha.) converting enzyme (TACE). All the substrates are prepared in 1:1 dimethyl sulfoxide (DMSO) and water. The stock solutions are 50-500. . .

L15 ANSWER 2 OF 50 USPATFULL

AB In one aspect of the invention, there is provided a method and apparatus for early detection of subacute, potentially catastrophic illness in a patient. The method comprises: (a) monitoring heart rate variability in the patient; and (b) identifying at least one characteristic abnormality in the heart rate variability that is associated with the illness. This method can be use to diagnose illnesses such as, but not limited to, sepsis, **necrotizing enterocolitis**, pneumonia and meningitis, as well as noninfectious illnesses. In another aspect of the present invention, there is provided a method and apparatus for early detection of subacute, potentially catastrophic illness in a patient.

The method comprises: (a) monitoring the patient's RR intervals; (b) generating a normalized data set of the RR intervals; (c) calculating one or more of (i) moments of the data set selected from the second and higher moments, including the standard deviation (ii) percentile values of the data set, (iii) sample entropy, and (iv) sample asymmetry; and (d) identifying an abnormal heart rate variability associated with the illness based on one or more of the moments, the percentile values, sample entropy, and sample asymmetry analysis.

ACCESSION NUMBER: 2002:99654 USPATFULL
TITLE: Method and apparatus for the early diagnosis of subacute, potentially catastrophic illness
INVENTOR(S): Griffin, M. Pamela, Charlottesville, VA, UNITED STATES
Moorman, J. Randall, Charlottesville, VA, UNITED STATES
Kovatchev, Boris P., Amherst, VA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002052557	A1	20020502
APPLICATION INFO.:	US 2001-793653	A1	20010227 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-770653, filed on 29 Jan 2001, PENDING Continuation of Ser. No. US 1999-271279, filed on 17 Mar 1999, GRANTED, Pat. No. US 6216032

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-78319P	19980317 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KENYON & KENYON, 1500 K STREET, N.W., SUITE 700, WASHINGTON, DC, 20005
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Page(s)
LINE COUNT: 1110

AB . . . is associated with the illness. This method can be use to diagnose illnesses such as, but not limited to, sepsis, **necrotizing enterocolitis**, pneumonia and meningitis, as well as noninfectious illnesses. In another aspect of the present invention, there is provided a method. . .

SUMM . . . 44, pp. 1-88 (1996). Survival of this group has improved with advances in neonatal intensive care, but late-onset sepsis and **necrotizing enterocolitis** ("NEC") continue to be major causes of morbidity and mortality. Stoll B. J., Gordon T., Korones S. B., Shankaran S., Tyson J. E., Bauer C. R., "Late-onset Sepsis in Very Low Birth Weight **Neonates**: A Report from the National Institute of Child Health and Human Development Neonatal Research Network," Journal of Pediatrics; 129:63-71 (1996);. . . Weight Infants: Relation to Admission Illness Severity, Resource Use, and Outcome," Pediatrics, 95:225-230 (1995). Unfortunately these illnesses are common in **neonates**, and infected infants have a significant increase in the number of days spent on the ventilator and an average increase. . .

SUMM . . . M. L., A. DeToni, I. Stolfi, M. P. Carrieri, M. Braga, and C. Zunin, "Risk Factors for Nosocomial Sepsis in **Newborn** Infants and Intermediate Care Units," European Journal of Pediatrics; 155:315-322 (1996). The National Institute of Child Health & Human Development ("NICHD") Neonatal Research Network found that

neonates who develop late-onset sepsis have a 17% mortality rate, more than twice the 7% mortality rate of noninfected infants.

SUMM [0006] **Necrotizing enterocolitis** affects up to 4,000 infants in the U.S. yearly, and an estimated 10 to 50% of infants who develop NEC die. Neu, J., "**Necrotizing Enterocolitis**," Pediatric Clinics of North America 43:409-432 (1996). Infants who develop NEC often require intubation and an increase in respiratory support.. . .

SUMM . . . sepsis is difficult (Escobar, G. J, "The Neonatal "Sepsis Work-up": Personal Reflections on the Development of an Evidence-Based Approach Toward **Newborn** Infections in a Managed Care Organization," Pediatrics, 103:360-373 (1999)), as the clinical signs are neither uniform nor specific. Because of. . . of antibiotics to infants without bacterial infection, and many unnecessary interruptions in neonatal nutrition. Moreover, despite these practices, sepsis and **necrotizing enterocolitis** continue to occur and continue to cause neonatal deaths. Indeed, by the time clinical signs and symptoms for either sepsis. . .

SUMM . . . Birth to Two Months of Age," Pediatric Infectious Disease Journal, 16:381-385 (1997)), as is often the practice in critically ill **newborn** infants. For example, as many as 60% of culture results may be falsely negative if only 0.5 mL blood is. . . J. K. Reynolds, S. D. Allen, J. A. Lemons, and P. L. Yu, "Volume of Blood Submitted for Culture from **Neonates**," Journal of Clinical Microbiology, 24:353-356 (1986). It is suspected that 30-40% of all infants with sepsis have negative blood cultures.. . .

SUMM . . . S. Dulkerian, L. McCawley, L. Corcoran, S. Butler, and L. Kilpatrick, "Cytokine Elevations in Critically Ill Infants with Sepsis and **Necrotizing Enterocolitis**," J. Pediatr., 124:105-111 (1994); Glauser, M. P., D. Heumann, J. D. Baumgartner, and J. Cohen, "Pathogenesis and Potential Strategies for. . . may interfere with normal events of Heartrate ("HR") control by the sympathetic and parasympathetic nervous systems. For example, the cytokines **TNF**-.alpha., IL-1.beta. and IL-6 increase HR, but they blunt HR responses to .beta.-adrenergic agonists. Oddis, C. V. and M. S. Finkel,. . .

SUMM . . . for every one infant that has a positive blood culture. Gerdes, J. S. and R. A. Polin, "Sepsis Screen in **Neonates** with Evaluation of Plasma Fibronectin," Pediatric Infectious Disease Journal, 6:443-446 (1987). Thus, a successful surveillance strategy which leads to an earlier diagnosis of potentially catastrophic illnesses such as sepsis and NEC as well as non-infectious illnesses in **neonates** and premature **newborns** is necessary and critical in decreasing mortality and morbidity. Moreover, such a surveillance strategy is also useful for detecting potentially. . .

SUMM . . . HRV is abnormal during illness, physicians have traditionally measured HRV as an indication of such illnesses. For example, in healthy **newborn** infants, time series of heart period (or RR intervals, the time between successive heart beats) show obvious variability. Numerous publications. . .

SUMM . . . sympathetic and parasympathetic arms of the autonomic nervous system, which act respectively to speed or slow the heart rate. In **newborn** infants, as in adults, HRV is substantially reduced during severe illness. Burnard, E. D., "Changes in Heart Size in the Dyspnoeic **Newborn** Infant." Brit Med J 1:1495-1500 (1959); Rudolph, A. J., C. Vallbona, and M. M. Desmond, "Cardiodynamic Studies in the **Newborn**, III. Heart Rate Patterns in Infants with

Idiopathic Respiratory Distress Syndrome," Pediatrics 36:551-559 (1965);
Cabal, L. A., B. Siassi, B.. . .

SUMM . . . HRV measurements, and thus is useful as a means of early diagnosis of potentially catastrophic illnesses such as sepsis and **necrotizing enterocolitis**. These novel measures thus serve to quantify well-established markers of early fetal and neonatal distress, and they add to clinical. . .

DETD [0023] This method can be used to diagnose illnesses such as, but not limited to, sepsis, **necrotizing enterocolitis**, pneumonia and meningitis, as well as non-infectious illnesses.

DETD . . . patient illness such that a decrease in HRV occurs before clinical manifestations of potentially catastrophic illnesses such as sepsis and **necrotizing enterocolitis** appear.

DETD . . . in patient populations that are at high risk of potentially catastrophic impending events such as, but not limited to, sepsis, **necrotizing enterocolitis**, pneumonia and meningitis, as well as non-infectious illnesses. Generally, the method is applicable for diagnosis of illnesses that lead to. . . intracranial hemorrhage.

Patient populations include patients at any life stage, including but not limited to low birth weight infants, premature **neonates**, **newborn** infants, infants, toddlers, children, adolescents, and adults.

DETD . . . Ideally, these parameters will be based on the results of a large group of patients, for example, a group of **newborn** patients at risk of sepsis and **necrotizing enterocolitis**. For example, from the infants observed to date, reasonable threshold values include: skewness on the order of about 1 or. . .

CLM What is claimed is:

12. The method of claim 8 wherein the patient is a **neonate**.

L15 ANSWER 3 OF 50 USPATFULL

AB Methods are described for preventing and treating **necrotizing enterocolitis** in animals, including humans. Antibodies directed to PAF and/or **TNF** are shown to have a beneficial effect in animal models predictive of human therapy for the treatment of **necrotizing enterocolitis**, which is a major life-threatening illness in **neonates** worldwide.

ACCESSION NUMBER: 2002:54357 USPATFULL

TITLE: Prevention and treatment of **necrotizing enterocolitis**

INVENTOR(S): Kink, John A., Madison, WI, UNITED STATES
Worledge, Katherine L., Middleton, WI, UNITED STATES

PATENT ASSIGNEE(S): Promega Corporation, Madison, WI, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002031516	A1	20020314
APPLICATION INFO.:	US 2001-832233	A1	20010410 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-318109, filed on 24 May 1999, GRANTED, Pat. No. US 6214343

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: MEDLEN & CARROLL, LLP, 220 Montgomery Street, Suite 2200, San Francisco, CA, 94104

NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 883
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Prevention and treatment of **necrotizing enterocolitis**
AB Methods are described for preventing and treating **necrotizing enterocolitis** in animals, including humans. Antibodies directed to PAF and/or **TNF** are shown to have a beneficial effect in animal models predictive of human therapy for the treatment of **necrotizing enterocolitis**, which is a major life-threatening illness in **neonates** worldwide.
SUMM [0001] The present invention relates to therapeutics for the prevention and treatment of **necrotizing enterocolitis**, and in particular the prevention and treatment of **necrotizing enterocolitis** in **neonates** through the use of antibody therapy.
SUMM [0002] **Necrotizing enterocolitis** (NEC) has emerged as the most common gastrointestinal emergency in neonatal intensive care units (NICU). A. M. Kosloske, "Epidemiology of **necrotizing enterocolitis**," Acta Paediatr. Suppl. 396:2 (1994). U. G. Stauffer, "**Necrotizing enterocolitis**," Acta Paediatr 83:666 (1994). NEC can occur endemically as isolated cases, or at times, epidemic clusters of cases are seen. . . 1 to 3 per 1000 live births and roughly 1 to 7.7% of NICU admissions. R. C. Holman et al., "**Necrotizing Enterocolitis** Mortality in the United States, 1979-85" AJPH 79:8 (1989). The average annual mortality rate for NEC was 13.1 deaths per 100,000 live births. In the United States, about 12,000 **newborn** infants per year develop NEC, with a mortality rate of up to 40%. Clinically, NEC is characterized by a triad. . . and tenderness, gastrointestinal bleeding, and pneumatosis intestinalis, i.e., air within the intestinal wall. R. M. Kliegman and A. A. Fanaroff, "**Necrotizing Enterocolitis**" New Eng. J. Med. 310:1093 (1984). Death associated from NEC occurs from intestinal perforation with sepsis with shock, intravascular dissemination,. . .
SUMM . . . immaturity (2) infection, (3) oral feeding and (4) hypoxia. A. M. Kosloske, "A unifying hypothesis for pathogenesis and prevention of **necrotizing enterocolitis**" J. Pediatrics 117:S68 (1990). It is thought that an opportunistic member of the infants microbial flora in combination with tissue. . . a series of host responses and stimulate the production of proinflammatory phospholipids and/or cytokines such as platelet activating factor (PAF), **tumor necrosis factor** (**TNF**) and interleukins 1 and 6 (IL-1 and IL-6). W. Hsueh et al., "Interaction of Inflammatory Cytokines, Bacterial Products, and Lipid. . .
SUMM . . . ticarcillin in combination with a second parenteral aminoglycoside such as gentamycin is then usually given. Ch. Fast and H. Rosegger, "**Necrotizing enterocolitis** prophylaxis, oral antibiotics and lyophilized entero-bacteria vs oral immunoglobulins" Acta Paediatr Suppl 396:86 (1994). Treatment periods typically last for 3. . .
SUMM . . . administered orally to low-birth weight infants has been reported to have some benefit. M. M. Eibl et al., "Prevention of **Necrotizing Enterocolitis** in Low-Birth-Weight Infants

by IgA-IgG Feeding" New Eng. J. Med. 319:1 (1988). H. M. Wolf and M. M. Eibl, "The Relevance of Immunoglobulin in the Prevention of **Necrotizing Enterocolitis**," In: Immunology of Milk and the **Neonate** (Plenum Press, NY 1991). H. M. Wolf and M. M. Eibl, "The anti-inflammatory effect of an oral immunoglobulin (IgA-IgG) preparation and its possible relevance for the prevention of **necrotizing enterocolitis**," Acta Paediatr Suppl. 396:37 (1994).

SUMM [0008] Recent studies have suggested that certain proinflammatory molecules including PAF, LPS and cytokines such as, **TNF** and IL-6 play an important role in the development of NEC in the **newborn**. Patients with NEC were reported to have higher levels of **TNF**, IL-1 and IL-6. D. Birk et al., "Is the elimination of endotoxin and cytokines with continuous lavage an alternative procedure in **necrotizing enterocolitis**?" Acta Paediatr Suppl. 396:24 (1994). Animal models for NEC indicate that the pathology associated with NEC can be generated by. . . endogenous mediator for bowel necrosis in endotoxemia," FASEB J. 1:403-405 (1987). X. Sun and W. Hsueh, "Bowel Necrosis Induced by **Tumor Necrosis Factor** in Rats Is Mediated by Platelet-activating Factor," J. Clin. Invest. 81:1328 (1988). Pretreatment of animals with a PAF antagonist, PAF-AH,. . . development of NEC. M. Caplan et al., "The Role of Recombinant Platelet-Activating Factor Acetylhydrolase in a Neonatal Rat Model of **Necrotizing Enterocolitis**," Ped. Research 42:779 (1997). Interestingly, human milk has significant PAF-AH activity, whereas neonatal formulas have no measurable PAF-AH enzyme function. This difference may contribute to the lower incidence of NEC in breast milk-fed **neonates**.

SUMM . . . encompassing the segment of the world population that has an increased risk for NEC. NEC is most commonly found in **neonates**, and in particular **neonates** in their first month of life and/or **neonates** with low birthweight (e.g., **neonates** weighing less than approximately 1,500 grams). **Neonates** with highest risk for NEC have been reported to be **neonates** weighing between approximately 750 and approximately 1,000 grams. T. L. Black et al., "**Necrotizing Enterocolitis**: Improving Survival Within a Single Facility," S. Med. Journal 82:1103 (1989).

SUMM [0014] The present invention relates to therapeutics for the prevention and treatment of **necrotizing enterocolitis**, and in particular the prevention and treatment of **necrotizing enterocolitis** in **neonates** through the use of antibody therapy. The examples of the present invention demonstrate a novel finding that antibodies against PAF or antibodies against **TNF** are effective (as demonstrated in an experimental model of NEC) in preventing NEC.

SUMM . . . the present invention contemplates a method comprising the administration of antibodies which bind to inflammatory mediators such as PAF or **TNF**. Preferably, the antibody is reactive with PAF or **TNF** across species. Specifically, the present invention demonstrates that immunization with human **TNF** generates neutralizing antibody capable of reacting with endogenous murine **TNF**. Thus, the present invention provides anti-**TNF** antibody that will react with mammalian **TNF** generally. In another embodiment, the antibodies are combined with other reagents (including but not limited to other antibodies).

SUMM [0018] In another embodiment, the present invention contemplates a method of treating **neonates** at risk for NEC. For example, the present invention contemplates a method of treatment, comprising: (a) providing: i) a **neonate** at risk for **necrotizing**

enterocolitis; ii) a therapeutic preparation, comprising anti-PAF antibodies and (b) administering said antibodies to said **neonate** (e.g., administering to the intestinal lumen of said **neonate**). In another embodiment, the present invention contemplates a method of treatment, comprising: (a) providing: i) a **neonate** at risk for **necrotizing enterocolitis** ; ii) a therapeutic preparation, comprising anti-**TNF** antibodies and (b) administering said antibodies to said **neonate** (e.g., administering to the intestinal lumen of said **neonate**).

SUMM . . . the symptoms of NEC. In one embodiment, the present invention contemplates a method of treatment, comprising: (a) providing: i) a **neonate** with symptoms of **necrotizing enterocolitis**; ii) a therapeutic preparation, comprising anti-PAF antibodies and (b) administering said antibodies to said **neonate** (e.g., administering to the intestinal lumen of said **neonate**) under conditions wherein at least one of said symptoms is reduced. In another embodiment, the present invention contemplates a method of treatment, comprising: (a) providing: i) a **neonate** with symptoms of **necrotizing enterocolitis**; ii) a therapeutic preparation, comprising anti-**TNF** antibodies and (b) administering said antibodies to said **neonate** (e.g., administering to the intestinal lumen of said **neonate**) under conditions wherein at least one of said symptoms is reduced.

SUMM [0020] The present invention relates to therapeutics for the prevention and treatment of **necrotizing enterocolitis**, and in particular the prevention and treatment of **necrotizing enterocolitis** in **neonates** through the use of avian polyclonal antibody therapy. More specifically, the present invention contemplates prevention and treatment of **necrotizing enterocolitis** in **neonates** through the administration (e.g., oral administration) of antibodies to cytokines and other inflammatory mediators.

SUMM . . . particular mediator. A variety of these mediators can be used to generate antibodies useful in the prevention and treatment of **necrotizing enterocolitis**. Illustrative inflammatory mediators are set forth in Table 1.

SUMM [0022] While not limited to particular inflammatory mediator, the preferred antibodies are directed to PAF and/or **TNF**. The present invention contemplates treatments

TABLE 1

Name	Abbr.	Type	Specific Name
Interferons	IFN	alpha	Leukocyte Interferon
		beta	Fibroblast Interferon
		gamma	Macrophage. . . Chemotactic Protein
	IL-9		Megakatyoblast Growth Factor
	IL-11		Stromal Cell-Derived Cytokine
	IL-12		Natural Killer Cell Stimulatory Factor
	IL-15		T-cell Growth Factor
Tumor Necrosis Factors	**TNF**	alpha	Cachectin
		beta	Lymphotoxin
Colony Stimulating Factors	CSF	GM-CSF	Granulocyte-macrophage Colony-Stimulating Factor
		Mp-CSF	Macrophage Growth Factor
		G-CSF	Granulocyte Colony-stimulating Factor
		EPO	Erythropoietin
Trans-. . .			

SUMM [0023] comprising anti-PAF antibodies and/or anti-**TNF** antibodies prior to and after onset of symptoms of NEC. In accordance with the present invention, antibody formulations are administered. . . these methods of administration. The antibodies can be used alone (e.g., anti-PAF alone) or in combination (e.g., anti-PAF together with anti-**TNF**- or another antibody to one of the above-described mediators).

DETD Production of Antibodies to **TNF** in the Hen

DETD [0036] This example involved (a) preparation of the immunogen and immunization, (b) purification of anti-**TNF** chicken antibodies from egg yolk (IgY), and (c) detection of anti-**TNF** antibodies in the purified IgY preparations.

DETD [0037] (a) Preparation of the immunogen and immunization. Recombinant human **Tumor Necrosis Factor** Alpha, (**TNF**) was purchased (lyophilized without bovine serum albumin (BSA) and designated carrier-free) from R&D Systems Inc., Minneapolis, Minn. and produced in E. coli. The lyophilized **TNF** was reconstituted in phosphate-buffered saline pH 7.2-7.5 (PBS) at 50 .mu.g/ml and from 2-10 .mu.g of **TNF** was used to immunize each hen. Each hen received one 0.5 ml sub-cutaneous injection containing **TNF** with 75 .mu.g Quil A adjuvant (Superfos Biosector, Denmark, distributed by Accurate Chem., Westbury, N.Y.) in PBS. The hens were.

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DETD [0038] (b) Purification of anti-**TNF** chicken antibodies from egg yolk (IgY). Groups of eggs were collected per immunization group at least 3-5 days after the. . .

DETD [0039] (c) Detection of anti-**TNF** antibodies in the purified IgY preparations. In order to determine if anti-**TNF** response was generated and to determine relative levels of the response, enzyme-linked immunosorbent assays (ELISA) were performed. Briefly, ninety-six well Falcon Pro-bind micro-titer plates were coated overnight at 4.degree. C. with 100 .mu.l well of **TNF** at 0.1-1.0 .mu.g/ml PBS. The wells are then blocked with PBS containing 1% BSA and 0.05% Tween 20 and incubated. . .

DETD [0040] The level of antibody response in the hens against **TNF**, given the low amounts of antigen used for immunization, indicates that this protein is very immunogenic in the hens and is a well-suited system to generate anti-mammalian **TNF** antibodies.

DETD Anti-**TNF** Cell Neutralization Assay

DETD [0047] This example demonstrates the neutralization capabilities of the anti-**TNF** IgY antibodies in an in vitro cell based bioassay. The cytolytic effect of **TNF** on the murine cell line L929 (ATCC CCL 1) in the presence of actinomycin D was previously described by Mathew,. . . M. J. Clemens, A. G. Morris and A. J. H Gearing, eds. IRL. Press. P.221. In the presence of neutralizing anti-**TNF**, **TNF** mediated cell death in the L929 cells should be prevented. L929 cells were grown in sterile conditions with Ham's F12. . . into the wells of a 96-well plate (Coming) and incubated 24 hours at 37(C., 5% CO.sub.2, in a humidified atmosphere. Anti-**TNF** IgY and preimmune IgY, were serially diluted and added to recombinant human **TNF** at 1.0 ng/ml (R&D Systems, MN) with 10 .mu.g/ml actinomycin D (ICN Biomedicals, Inc., Ohio) for 1 hour. After addition to the cells, the final concentrations of antibodies, **TNF**, and actinomycin D in each well were 1.0-0.002 .mu.g/ml, 0.05 ng/ml, and 1.0 .mu.g/ml respectively. After approximately 20 hours, cell. . . the dye solution and measuring the OD at 490 nm. See Table 2 below.

TABLE 2

Antibody Concentration (.mu.g/ml)	Percent Neutralization Anti-**TNF** IgY
1.0	94 (+/-) 12%
0.5	96 (+/-) 10%
0.25	85 (+/-) 7%
0.12	87 (+/-) 3%
0.062	90 (+/-) 16%
0.031	85 (+/-) 7%
0.016	33. . .

DETD [0048] As is seen in the table above, the amount of anti-**TNF** which resulted in prevention of cell death in 50% of the cells was measured at 20 ng/ml. There was no measurable neutralization of the **TNF** at any concentration (1.0 .mu.g/ml-0.002 .mu.g/ml) using the preimmune IgY. These results indicate that avian anti-**TNF** is quite effective at neutralizing the effects of **TNF** in this cell-based assay.

DETD [0050] In order to determine whether anti-**TNF** or anti-PAF polyclonal antibodies are capable of neutralizing the effects of bowel necrosis in vivo, a rodent model of **necrotizing enterocolitis** was utilized. This model uses PAF to simulate intestinal necrosis which is characterized by the gross and histological pathological features similar to those found in adult patients with ischemic bowel disease or in **neonates** with NEC. (See F. Gonzalez-Cruzzi and W. Hsueh, Am J Pathol, 112:127-135 (1993)). To induce bowel necrosis, rats are systemically. . .

DETD Prevention of Acute Bowel Necrosis in Vivo by the Administration of Avian Polyclonal Anti-**TNF** or Anti-PAF

DETD [0054] The rat model described in Example 5 was used to determine whether the avian anti-**TNF** or anti-PAF is effective at preventing lethality and bowel necrosis induced by PAF. Rats were pretreated either parenterally (i.p.) or. . . were then assessed in the different treatment groups 2 hours post-PAF challenge. This example involves: (a) Pretreatment studies were the anti-**TNF** or anti-PAF is administered parenterally before PAF challenge. (b) Pretreatment studies were the anti-**TNF** or anti-PAF is administered orally before PAF challenge

DETD . . . were conducted to determine if the adverse effects induced by PAF in the rats could be prevented using either avian anti-**TNF** or anti-PAF when administered parenterally. Treatment groups consisted of rats treated with: a) vehicle (0.1 M carbonate pH 9.5); b) preimmune IgY; c) anti-**TNF**; and d) anti-PAF. In some experiments, normal rats were not treated with PAF and were either untreated (Normal control) or. . . toxicity before the two hour time point were immediately necropsied and small bowel morbidity was also scored. The ability of anti-**TNF** or anti-PAF to prevent mortality and small bowel pathology (morbidity) in the rats is shown in Table 3. The cumulative. . .

DETD . . . out of a maximum of 4. In contrast, both groups of PAF treated rats that were i.p. pretreated either with anti-**TNF** or anti-PAF showed a marked reduction of small bowel morbidity with no mortality from PAF toxicity. These results indicate that the parenteral pretreatment of either anti-**TNF** or anti-PAF is effective at preventing bowel necrosis in this model *(p value<0.05 for both anti-**TNF** and anti-PAF morbidity scores as compared to vehicle or preimmune controls).

TABLE 3

	No. Of	No. Of	% Cumulative. . . 1	Cumulative 1
0				
0				
2) Treated controls	1	4	0	0
3) Vehicle	4	6	33	3.5
4) Preimmune	5	10	10	3.6
5) Anti-**TNF**	5	10	0	1.5*
6) Anti-PAF	5	11	0	1.3*

DETD . . . Normal control 1 1 1.0 (+/-) 0.0

2) Treated control	1	4	1.0 (+/-) 0.0
3) Pre-immune	2	7	2.3 (+/-) 0.5
4) Anti-**TNF**	1	5	2.1 (+/-) 0.2
5) Anti-PAF	2	7	1.6 (+/-) 0.5*

DETD . . . anti-PAF delivered intraperitoneally, significantly reduced the microscopic histological damage as compared to the preimmune treated controls (p value<0.05). However, the anti-**TNF** had only a slightly protective effect as compared to the preimmune control (p value>0.05). These results indicate that the anti-PAF. . .

DETD . . . studies, experiments were conducted to determine if PAF induced bowel necrosis in the rats can be prevented using either avian anti-**TNF** or anti-PAF when administered orally. Treatment groups consisted of rats treated with: a) vehicle (0.1 M carbonate pH 9.5); b) preimmune IgY; c) anti-**TNF**; and d) anti-PAF. As described in Example 6 (a), some normal rats were not treated with PAF and were either. . . tail vein with 100 ul of saline containing 1.2 ug of PAF as described above. The ability of orally administered anti-**TNF** or anti-PAF to prevent mortality and small bowel pathology (morbidity) in the rats two hours after PAF treatment was assessed. . . 1

1	0	0		
2) Treated control	1	3	0	0
3) Vehicle	1	3	0	4.0
4) Preimmune	4	11	45	3.4
5) Anti-**TNF**	2	6	0	0.8*
6) Anti-PAF	3	10	0	0.6*

DETD . . . IgY and the small bowel gross appearance was identical to that of the normal controls. Groups orally pretreated either with anti-**TNF** or anti-PAF were effectively treated against PAF toxicity. Both groups showed a significant reduction in small bowel morbidity with no mortality from PAF toxicity. Morbidity scores in the anti-**TNF** and anti-PAF treated groups had statistically significant lower average morbidity score of about 0.7, as compared to a score of. . . mortality in the preimmune-treated rats was very high. In contrast, both these results indicate that the oral pretreatment of either anti-**TNF** or anti-PAF is effective at preventing bowel necrosis in this model. These results also support the experiments where the parenteral pretreatment of anti-**TNF** or anti-PAF could effectively prevent bowel necrosis by PAF.The histological evaluation of specimens after sectioning and H&E staining were evaluated. . . 0.0

2) Treated control	1	3	1.0 (+/-) 0.0
2) Vehicle	1	3	2.3 (+/-) 0.6

3) Pre-immune 3 10 3.4 (+/-) 0.5
4) Anti-**TNF** 1 5 1.4 (+/-) 0.6*
5) Anti-PAF 3 10 1.3 (+/-) 0.5*

DETD [0061] As seen in table 5, the animals treated orally with anti-**TNF** and anti-PAF had significantly less histological damage as compared to the preimmune treated controls (p value<0.001). In fact, the histological scores for the anti-**TNF** and anti-PAF antibody treated animals approached the values seen for the normal control group.

These results indicate the potent ability. . .

CLM What is claimed is:

1. A method of treatment, comprising: a) providing: i) a human **neonate**, wherein said human **neonate** has symptoms of **necrotizing enterocolitis**; ii) a therapeutic formulation comprising polyclonal antibodies directed to **TNF**, and; b) administering said formulation to said human **neonate**.

9. A method of treatment, comprising: a) providing: i) a **neonate** at risk for **necrotizing enterocolitis**, ii) a therapeutic formulation comprising polyclonal antibody directed to **TNF**, and; b) administering said formulation to the lumen of the intestine of said **neonate**.

10. The method of claim 9, wherein said **neonate** is a low birth weight **neonate**.

IT Animal
IT Bird (Aves)
IT **Newborn**

(avian polyclonal antibodies against TNF or platelet activating factor for prevention and treatment of necrotizing enterocolitis esp. in neonate)

L15 ANSWER 4 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB Activation of microglia, the resident macrophages in the CNS, plays a significant role in neuronal death or degeneration in a broad spectrum of CNS disorders. Recent studies indicate that nanomolar concentrations of the serine protease, thrombin, can activate microglia in culture. However, in contrast to other neural cells responsive to thrombin, the participation of novel protease-activated receptors (PARs), such as the prototypic thrombin receptor PAR1, in thrombin-induced microglial activation was cast in doubt. In this report, by utilizing primary microglial cultures from PAR1 knockout (PAR1-/-) mice, application of the PAR1 active peptide TRAP-6 (SFLLRN) in comparison to a scrambled peptide (LFLNR), we have unambiguously demonstrated that murine microglia constitutively express PAR1 mRNA that is translated into fully functional protein. Activation of the microglial PAR1 induces a rapid cytosolic free [Ca(2+)](i) increase and transient activation of both p38 and p44/42 mitogen-activated protein kinases. Moreover, although in part, this PAR1 activation directly contributes to thrombin-induced microglial proliferation. Furthermore, although not directly inducing **tumor necrosis factor**-.alpha. (**TNF**-.alpha.) release, PAR1 activation up-regulates microglial CD40 expression and potentiates CD40 ligand-induced **TNF**-.alpha. production, thus indirectly contributing to microglial activation. Taken together, these results demonstrate an essential role of PAR1 in thrombin-induced microglial activation. In addition, strategies aimed at blocking thrombin signaling through PAR1 may be therapeutically valuable for diseases associated with

cerebral vascular damage and significant inflammation with microglial activation.

ACCESSION NUMBER: 2002268422 EMBASE
TITLE: Participation of protease-activated receptor-1 in thrombin-induced microglial activation.
AUTHOR: Suo Z.; Wu M.; Ameenuddin S.; Anderson H.E.; Zoloty J.E.; Citron B.A.; Andrade-Gordon P.; Festoff B.W.
CORPORATE SOURCE: Z. Suo, Neurobiology Research Laboratory, Veterans Affairs Medical Center, 4801 Linwood Blvd., Kansas City, MO 64128, United States. zsuo@kumc.edu
SOURCE: Journal of Neurochemistry, (2002) 80/4 (655-666).
Refs: 78
ISSN: 0022-3042 CODEN: JONRA
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB . . . protein kinases. Moreover, although in part, this PAR1 activation
directly contributes to thrombin-induced microglial proliferation. Furthermore, although not directly inducing **tumor necrosis factor**-.alpha. (**TNF**-.alpha.) release, PAR1 activation up-regulates microglial CD40 expression and potentiates CD40 ligand-induced **TNF**-.alpha. production, thus indirectly contributing to microglial activation. Taken together, these results demonstrate an essential role of PAR1 in thrombin-induced microglial. .
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CT Medical Descriptors:
*enzyme activation
*cell activation
*microglia
macrophage
nerve cell necrosis
nerve cell degeneration
cell culture
knockout mouse
protein expression
RNA translation
gene activation
calcium transport
calcium cell level
cell proliferation
cytokine production
signal transduction
inflammation
nonhuman
mouse
controlled study
animal cell
newborn
article
priority journal
*proteinase activated receptor 1
*thrombin
thrombin receptor
messenger RNA
calcium ion: EC, endogenous compound

synaptophysin: EC, endogenous compound
protein p44: EC, endogenous compound
protein p42: EC, endogenous compound
mitogen activated protein kinase: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound
CD40 antigen: EC, endogenous compound
ligand

L15 ANSWER 5 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB Background: **TNF**-.alpha. secreted by activated T cells is known to increase intestinal permeability, whereas transforming growth factor (TGF) .beta. has the ability to protect the epithelial barrier.
Objective:
We determined the expression of TGF-.beta.1, its receptors, and **TNF**-.alpha. on the mucosa of small intestine to investigate their roles in the pathogenesis of food protein-induced enterocolitis syndrome (FPIES). Methods: Twenty-eight infants diagnosed with FPIES by means of clinical criteria and challenge test results were included. Immunohistochemical stains for TGF-.beta.1, type 1 and 2 TGF-.beta. receptors, and **TNF**-.alpha. on duodenal biopsy specimens were performed. Results: TGF-.beta.1 expression was generally depressed in patients. Expression of type 1 TGF-.beta. receptor was significantly lower
in the patients who had villous atrophy compared with expression in those patients who did not ($P < .001$) and negatively correlated with the severity of atrophy ($r = -0.59$, $P < .001$). Expression of type 2 TGF-.beta.
receptor showed no significant difference between the patients with or without villous atrophy. The immunoreactivity for both TGF-.beta. receptors on lamina proprial cells was slight or negative. **TNF**-.alpha. expression was detected on both epithelial and lamina proprial cells and was significantly greater in the patients who had villous atrophy compared with that in the patients who did not ($P < .01$).
Conclusion: Our results suggest that decreased countering activity of TGF-.beta.1 against T-cell cytokines is implicated in the pathogenesis of FPIES. The significantly lower expression of type 1 TGF-.beta. receptor compared with type 2 receptor suggests the differential contribution of each receptor to the diverse biologic activities of TGF-.beta. in the intestinal epithelium.

ACCESSION NUMBER: 2002048132 EMBASE
TITLE: Expression of transforming growth factor .beta.1, transforming growth factor type I and II receptors, and **TNF**-.alpha. in the mucosa of the small intestine in infants with food protein-induced enterocolitis syndrome.
AUTHOR: Hai L.C.; Jin B.H.; Jeong J.P.; Sang G.K.
CORPORATE SOURCE: Dr. L.C. Hai, Department of Pediatrics, School of Medicine,
Catholic University of Taegu, 3056-6 Taemyung 4 Dong Namgu,
Taegu 705-034, Korea, Republic of
SOURCE: Journal of Allergy and Clinical Immunology, (2002) 109/1 (150-154).
Refs: 25
ISSN: 0091-6749 CODEN: JACIBY
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
007 Pediatrics and Pediatric Surgery
048 Gastroenterology
LANGUAGE: English

SUMMARY LANGUAGE: English

TI Expression of transforming growth factor .beta.1, transforming growth factor type I and II receptors, and **TNF**-.alpha. in the mucosa of the small intestine in infants with food protein-induced enterocolitis syndrome.

AB Background: **TNF**-.alpha. secreted by activated T cells is known to increase intestinal permeability, whereas transforming growth factor (TGF) .beta. has the ability to protect the epithelial barrier.

Objective:

We determined the expression of TGF-.beta.1, its receptors, and **TNF**-.alpha. on the mucosa of small intestine to investigate their roles in the pathogenesis of food protein-induced enterocolitis syndrome (FPIES). Methods:. . . of clinical criteria and challenge test results were included. Immunohistochemical stains for TGF-.beta.1, type 1 and 2 TGF-.beta. receptors, and **TNF**-.alpha. on duodenal biopsy specimens were performed. Results: TGF-.beta.1 expression was generally depressed in patients. Expression of type 1 TGF-.beta. receptor. . . patients with or without villous atrophy. The immunoreactivity for both TGF-.beta. receptors on lamina proprial cells was slight or negative. **TNF**-.alpha. expression was detected on both epithelial and lamina proprial cells and was significantly greater in the patients who had villous. . .

CT Medical Descriptors:

*small intestine mucosa
***enterocolitis**
*food protein induced enterocolitis syndrome
*immunohistochemistry
T lymphocyte
provocation test
duodenum biopsy
intestine villus atrophy
clinical feature
diarrhea
vomiting
fever
failure to thrive
abdominal distension
human
clinical article
newborn
infant
article
priority journal
*transforming growth factor beta1: EC, endogenous compound
*transforming growth factor beta receptor: EC, endogenous compound
***tumor necrosis factor alpha: EC, endogenous compound**

L15 ANSWER 6 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB Pontosubicular neuron necrosis (PSN) represents an age-specific response to severe hypoxic-ischemic injury occurring in human **neonates** but not in older children or adults. Histologically, PSN is characterized by acute neuronal death in the pontine nuclei and the hippocampal subiculum bearing the hallmarks of apoptosis. In animal models of hypoxic-ischemic injury, induction of neuronal apoptosis can be triggered by Fas (CD95/Apo-1), a cell surface receptor of the **tumor necrosis factor**-.alpha. superfamily, which transduces apoptotic death signals when crosslinked by its natural ligand. Here, we have investigated the expression of Fas/Fas ligand in human autopsy material consisting of 13 PSN cases and 10 age-matched cases without PSN. Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling,

immunohistochemistry, and double labeling for Fas/Fas ligand and the astrocyte marker glial fibrillary acid protein, the microglia/macrophage specific marker KiM1P, and the neuronal marker NeuN were performed on formalin-fixed brain specimens. Although mainly neurons of both PSN and controls expressed Fas receptor, expression was significantly increased (p = 0.001) in PSN cases in which predominantly degenerating cells with signs of early apoptosis showed Fas expression. In contrast, Fas ligand expression was found mainly on astrocytes and microglial cells. There was no significant difference between cases with and without PSN. We conclude that in the developing human brain, cells expressing the Fas receptor may be susceptible to undergoing apoptosis in response to hypoxic-ischemic injury.

ACCESSION NUMBER: 2002043410 EMBASE
TITLE: Fas (CD95/Apo-1)/Fas ligand expression in **neonates** with pontosubicular neuron necrosis.
AUTHOR: Van Landeghem F.K.H.; Felderhoff-Mueser U.; Moysich A.; Stadelmann C.; Obladen M.; Bruck W.; Buhrer C.
CORPORATE SOURCE: U. Felderhoff-Mueser, Department of Neonatology, Campus Virchow Klinikum, Humboldt University, Augustenburger Platz 1, D-13353 Berlin, Germany. ursula.felderhoff@charite.de
SOURCE: Pediatric Research, (2002) 51/2 (129-135).
Refs: 40
ISSN: 0031-3998 CODEN: PEREBL
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English

TI Fas (CD95/Apo-1)/Fas ligand expression in **neonates** with pontosubicular neuron necrosis.

AB Pontosubicular neuron necrosis (PSN) represents an age-specific response to severe hypoxic-ischemic injury occurring in human **neonates** but not in older children or adults. Histologically, PSN is characterized by acute neuronal death in the pontine nuclei and. . . models of hypoxic-ischemic injury, induction of neuronal apoptosis can be triggered by Fas (CD95/Apo-1), a cell surface receptor of the **tumor necrosis factor**-.alpha. superfamily, which transduces apoptotic death signals when crosslinked by its natural ligand. Here, we have investigated the expression of Fas/Fas. . .

CT Medical Descriptors:
***nerve cell necrosis**
brain hypoxia
brain ischemia
apoptosis
cross linking
signal transduction
nick end labeling
immunohistochemistry
astrocyte
microglia
human
male
female
clinical article
human tissue
human cell

newborn
article
priority journal
*FAS ligand: EC, endogenous compound
*Fas antigen: EC, endogenous compound
***tumor necrosis factor alpha: EC, endogenous compound**
*DNA nucleotidylexotransferase: EC, endogenous compound
*glial fibrillary acidic protein: EC, endogenous compound

L15 ANSWER 7 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AB The plaques in multiple sclerosis (MS) autopsy tissue contain **tumor necrosis factor**-.alpha. (**TNF**-.alpha.) at high concentrations. Moreover, microglia are able to convert L-tryptophan to quinolinic acid. Thus, **TNF**-.alpha. and quinolinic acid are endogenous compounds which may compromise oligodendrocytes during inflammatory demyelination. It is also known that cellular functions depend on adequate concentrations of glutathione (GSH).
As some apoptotic oligodendrocytes have been observed in MS plaques, it was therefore logical to determine whether oligodendrocyte apoptosis would occur in response to **TNF**-.alpha., quinolinic acid or GSH depletion. Oligodendrocytes were treated in vitro with **TNF**-.alpha., quinolinic acid and the GSH-depleting agent, buthionine sulfoximine (BSO), respectively, and the numbers of intact and apoptotic cells were counted. **TNF**-.alpha. reduced the numbers of mature oligodendrocytes, but not immature oligodendrocytes, without producing apoptosis. Quinolinic acid and BSO each caused oligodendrocyte loss via apoptosis, and GSH ethyl ester partly protected the cells against BSO. The data suggest that oligodendrocytes undergo apoptosis under adverse conditions that result from an endogenous toxicant or depletion of GSH.

ACCESSION NUMBER: 2002239320 EMBASE
TITLE: Apoptosis of oligodendrocytes in secondary cultures from neonatal rat brains.
AUTHOR: Cammer W.
CORPORATE SOURCE: W. Cammer, Department of Neurology, F-140, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, United States. wcammer@aecom.yu.edu
SOURCE: Neuroscience Letters, (19 Jul 2002) 327/2 (123-127).
Refs: 30
ISSN: 0304-3940 CODEN: NELED5
PUBLISHER IDENT.: S 0304-3940(02)00392-0
COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The plaques in multiple sclerosis (MS) autopsy tissue contain **tumor necrosis factor**-.alpha. (**TNF**-.alpha.) at high concentrations. Moreover, microglia are able to convert L-tryptophan to quinolinic acid. Thus, **TNF**-.alpha. and quinolinic acid are endogenous compounds which may compromise oligodendrocytes during inflammatory demyelination. It is also known that cellular functions. . . have been observed in MS plaques, it was therefore logical to determine whether oligodendrocyte apoptosis would occur in response to **TNF**-.alpha., quinolinic acid or GSH depletion. Oligodendrocytes were treated in vitro with **TNF**-.alpha., quinolinic acid and the GSH-depleting agent, buthionine

sulfoximine (BSO), respectively, and the numbers of intact and apoptotic cells were counted. **TNF**-.alpha. reduced the numbers of mature oligodendrocytes, but not immature oligodendrocytes, without producing apoptosis. Quinolinic acid and BSO each caused oligodendrocyte. . .

CT Medical Descriptors:
*apoptosis
*oligodendroglia
cell culture
cell maturation
cell protection
immunofluorescence
nerve cell necrosis
cell count
nonhuman
rat
controlled study
animal tissue
newborn
article
priority journal
tumor necrosis factor alpha
quinolinic acid
buthionine sulfoximine
glutathione ethyl ester
glutathione: EC, endogenous compound
platelet derived growth factor
fibroblast growth factor

L15 ANSWER 8 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB Concerns about sexual health, fertility, and pregnancy are common in patients with inflammatory bowel disease (IBD). Fertility is usually normal, although may be decreased in women with active Crohn's disease. Women with active IBD (especially Crohn's disease) are at risk of having small and premature babies. In some patients with IBD it may be desirable to continue drug treatment during pregnancy in order to control disease activity. Early engagement in discussion of these issues is important and it should be possible for most patients with IBD to have a normal outcome of pregnancy.

ACCESSION NUMBER: 2002032404 EMBASE
TITLE: Inflammatory bowel disease in pregnancy.
AUTHOR: Alstead E.M.
CORPORATE SOURCE: Dr. E.M. Alstead, Department of Adult and Paediatric, St. B. Royal London Sch./Med. Dent., Turner Street, London E1 2AD, United Kingdom. e.m.alstead@mds.qmw.ac.uk
SOURCE: Postgraduate Medical Journal, (2002) 78/915 (23-26).
Refs: 40
ISSN: 0032-5473 CODEN: PGMJAO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 010 Obstetrics and Gynecology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

CT Medical Descriptors:
*enteritis: EP, epidemiology
*pregnancy complication: CO, complication
sexuality
fertility

Crohn disease: DT, drug therapy
Crohn disease: EP, epidemiology
risk assessment
small for date infant
prematurity
disease activity
disease control
treatment outcome
congenital malformation: SI, side effect
teratogenicity: SI, side effect
neural tube defect: SI, side effect
systemic lupus erythematosus: SI, side effect
liver toxicity: SI, side effect
nephrotoxicity: SI, side effect
human
female
fetus
newborn
adult
review
*folic acid: DT, drug therapy
*aminosalicylic acid: DT, drug therapy
*mesalazine: AE, adverse drug reaction
*mesalazine: DT, drug therapy
*salazosulfapyridine: AE, adverse drug reaction
*salazosulfapyridine:. . . AE, adverse drug reaction
mercaptopurine: DT, drug therapy
cyclosporin: AE, adverse drug reaction
cyclosporin: DT, drug therapy
methotrexate: AE, adverse drug reaction
methotrexate: DT, drug therapy
tumor necrosis factor antibody: AE, adverse drug reaction
tumor necrosis factor antibody: DT, drug therapy
antibiotic agent: AE, adverse drug reaction
antibiotic agent: DT, drug therapy
metronidazole: AE, adverse drug reaction
metronidazole: DT,. . .

RN. . . 28088-64-4, 51540-64-8, 65-49-6, 80702-32-5; (mesalazine) 89-57-6; (salazosulfapyridine) 599-79-1; (azathioprine) 446-86-6; (mercaptopurine) 31441-78-8, 50-44-2, 6112-76-1; (cyclosporin) 79217-60-0; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (**tumor necrosis factor** antibody) 162774-06-3; (metronidazole) 39322-38-8, 443-48-1; (ciprofloxacin) 85721-33-1

L15 ANSWER 9 OF 50 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1

AB Methods are described for preventing and treating **necrotizing enterocolitis** in animals, including humans. Antibodies directed to platelet activating factor (PAF) and/or **TNF** are shown to have a beneficial effect in animal models predictive of human therapy for the treatment of **necrotizing enterocolitis**, which is a major life-threatening illness in **neonates** worldwide.

ACCESSION NUMBER: 2001:255200 CAPLUS
DOCUMENT NUMBER: 134:279576
TITLE: Prevention and treatment of **necrotizing enterocolitis**
INVENTOR(S): Kink, John A.; Worledge, Katherine L.
PATENT ASSIGNEE(S): Ophidian Pharmaceuticals, Inc., USA
SOURCE: U.S., 9 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6214343	B1	20010410	US 1999-318109	19990524
US 2002031516	A1	20020314	US 2001-832233	20010410

PRIORITY APPLN. INFO.: US 1999-318109 A1 19990524
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

TI Prevention and treatment of **necrotizing enterocolitis**

AB Methods are described for preventing and treating **necrotizing enterocolitis** in animals, including humans. Antibodies directed to platelet activating factor (PAF) and/or **TNF** are shown to have a beneficial effect in animal models predictive of human therapy for the treatment of **necrotizing enterocolitis**, which is a major life-threatening illness in **neonates** worldwide.

ST **necrotizing enterocolitis** polyclonal antibody **TNF** PAF; **neonate necrotizing enterocolitis** antibody platelet activating factor

IT Animal
Bird (Aves)
Newborn
(avian polyclonal antibodies against **TNF** or platelet activating factor for prevention and treatment of **necrotizing enterocolitis** esp. in **neonate**)

IT Antibodies
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(avian polyclonal antibodies against **TNF** or platelet activating factor for prevention and treatment of **necrotizing enterocolitis** esp. in **neonate**)

IT **Tumor necrosis factors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(avian polyclonal antibodies against **TNF** or platelet activating factor for prevention and treatment of **necrotizing enterocolitis** esp. in **neonate**)

IT Drug delivery systems
(oral; avian polyclonal antibodies against **TNF** or platelet activating factor for prevention and treatment of **necrotizing enterocolitis** esp. in **neonate**)

IT Drug delivery systems
(parenterals; avian polyclonal antibodies against **TNF** or platelet activating factor for prevention and treatment of **necrotizing enterocolitis** esp. in **neonate**)

IT Intestine, disease
(pseudomembranous enterocolitis; avian polyclonal antibodies against **TNF** or platelet activating factor for prevention and treatment of **necrotizing enterocolitis** esp. in **neonate**)

IT Drug delivery systems
(rectal; avian polyclonal antibodies against **TNF** or platelet activating factor for prevention and treatment of **necrotizing enterocolitis** esp. in **neonate**)

IT 65154-06-5, Platelet activating factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(avian polyclonal antibodies against **TNF** or platelet activating factor for prevention and treatment of **necrotizing**

enterocolitis esp. in **neonate**)

L15 ANSWER 10 OF 50 USPATFULL

AB Enteral formulas that contain long-chain polyunsaturated fatty acids (PUFAs), e.g., arachidonic acid (AA), and docosahexaenoic acid (DHA), essentially free of cholesterol, are described for use in methods for reducing the incidence of **necrotizing enterocolitis**. Compositions from egg yolk lipids are preferred as they contain .omega.-6 and .omega.-3 long chain PUFAs and are predominantly in a phosphtidylcholine form. This is believed to provide a synergetic effect.

ACCESSION NUMBER: 2001:185342 USPATFULL

TITLE: Methods for reducing the incidence of **necrotizing enterocolitis**

INVENTOR(S): Carlson, Susan E., Kansas City, MO, United States
Ponder, Debra L., Evansville, IN, United States
Montalto, Michael B., Columbus, OH, United States
Dohnalek, Margaret H., Worthington, OH, United States
Benson, John D., Powell, OH, United States
Borror, David A., Westerville, OH, United States
Diodato, David V., Hilliard, OH, United States

PATENT ASSIGNEE(S): Abbott Laboratories, Abbott Park, IL, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6306908	B1	20011023
APPLICATION INFO.:	US 2000-570299		20000512 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1997-943576, filed on 3 Oct 1997, now patented, Pat. No. US 6080787 Continuation-in-part of Ser. No. US 1997-804700, filed on 21 Feb 1997, now abandoned Continuation-in-part of Ser. No. US 1997-825314, filed on 28 Mar 1997, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Spivack, Phyllis G.
LEGAL REPRESENTATIVE: Brainard, Thomas D.
NUMBER OF CLAIMS: 27
EXEMPLARY CLAIM: 1
LINE COUNT: 1044
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Methods for reducing the incidence of **necrotizing enterocolitis**

AB . . . (AA), and docosahexaenoic acid (DHA), essentially free of cholesterol, are described for use in methods for reducing the incidence of **necrotizing enterocolitis**. Compositions from egg yolk lipids are preferred as they contain .omega.-6 and .omega.-3 long chain PUFAs and are predominantly in. . .

GOVI Some aspects of this invention were developed in the Neonatal Nursery of the University of Tennessee **Newborn** Center under the direction of Dr. Susan E. Carlson with financial support from the Ross Products Division of Abbott Laboratories. . .

SUMM **Necrotizing enterocolitis** (NEC) is a serious problem in infants having birth weights of less than about 1500 grams. Despite almost three (3). . ..

SUMM Flageole et al., Ngecrofizing Enterocolitts of the **Newborn**,

Review for the Clinician. Union-Med-Can. 1991 Sep-Oct; 120(5): 334-8, suggest the pathogenesis of NEC includes mesenteric ischemia, gastrointestinal immaturity, enteral. . .

SUMM Caplan et al., Role of Platelet Activating Factor and **Tumor Necrosis Factor**-Alpha in Neonatal **Necrotizing Enterocolitis**, Journal of Pediatrics, June, 1990, 960-964, report platelet activating factor and **tumor necrosis factor**-alpha are elevated in patients with NEC;

SUMM Kliegman et al., Clostridia as Pathogens in Neonatal **Necrotizing Enterocolitis**, The Journal of Pediatrics, August, 1979, 287-289, reports the isolation of Clostridia perfringens from children with neonatal NEC;

SUMM Eyal et al., **Necrotizing Enterocolitis** in the Very Low Birth Weight Infant: Expressed Breast Milk Feeding Compared with Parenteral Feeding, Archives of Disease in Childhood,. . .

SUMM Finer et al., Vitamin E and **Necrotizing Enterocolitis**, Pediatrics, Vol. 73, No. 3, March 1984 suggests that administration of vitamin E to reduce the incidence of severe sequelae. . .

SUMM Brown et al., Preventing **Necrotizing Enterocolitis** in **Neonates**, JAMA, Nov. 24, 1978, Vol. 240, No. 22, 2452-2454 reports that NEC can be virtually eliminated by the use of. . .

SUMM Kosloske, Pathogenesis and Prevention of **Necrotizing Enterocolitls**: A Hypothesis Based on Personal Observation and a Review of the Literature,

SUMM The present invention has many aspects. In a first aspect, the invention contemplates a method for reducing the incidence of **necrotizing enterocolitis** in an infant who is susceptible to **necrotizing enterocolitis**, said method comprising the administration of an effective amount of at least one long chain PUFA selected from the group. . .

SUMM . . . egg lecithin and egg phosphatidles. Thus, in a further aspect, the invention provides a method for decreasing the incidence of **necrotizing enterocolitis** in an infant, said method comprising feeding to said infant a sufficient quantity of an enteral nutritional composition containing protein,. . .

SUMM In another aspect, the invention provides a method for decreasing the occurrence of **necrotizing enterocolitis** in a human infant, said method comprising administering to the infant phospholipids in an amount effective to reduce the incidence of **necrotizing enterocolitis**.

SUMM In yet another aspect, the invention provides a method for decreasing the occurrence of **necrotizing enterocolitis** in a human infant, said method comprising administering to the infant choline in an amount effective to reduce the incidence of **necrotizing enterocolitis**.

SUMM More broadly, this aspect of the invention contemplates a method for reducing the incidence of **necrotizing enterocolitis** in an infant which is susceptible to **necrotizing enterocolitis**, said method comprising the administration of an effective amount of at least one long chain PUFA selected from the group. . .

SUMM There is further disclosed a method for decreasing the occurrence of **necrotizing enterocolitis** in a human infant, said method comprising administering to the infant egg phospholipids in an amount to result in at. . .

DETD . . . II and III were fed to infants in a study conducted in the

Neonatal Nursery of the University of Tennessee **Newborn** Center under the direction of Dr. Susan E. Carlson with financial support from Ross Products Division of Abbott Laboratories (Study. . .

DETD Findings: An unanticipated finding was that a higher incidence of **necrotizing enterocolitis** (NEC) was seen in the Control Groups than the Experimental Group. Table VI groups the total number of **neonates** according to treatment (Control v. Experimental) and sets forth the number of **neonates** in each group that developed NEC. NEC was considered present or suspect when clinical signs and symptoms consistent with this. . .

CLM What is claimed is:

1. A method for reducing the incidence of **necrotizing enterocolitis** in an infant, said method comprising administering to an infant which is susceptible to **necrotizing enterocolitis** an effective amount of a composition comprising protein, carbohydrate and lipid, including at least 1.0 mg of .omega.-6 polyunsaturated fatty. . .

16. The method according to claim 1 comprising feeding to an infant which is susceptible to **necrotizing enterocolitis** a sufficient amount of an enteral formula containing: protein, carbohydrate and phospholipids, said phospholipids providing arachidonic acid and docosahexaenoic acid. . .

17. A method for providing nutrition to an infant susceptible to or having **necrotizing enterocolitis**, said method comprising enterally administering to said infant an effective amount of at least one .omega.-6 polyunsaturated fatty acid in. . .

26. The method according to claim 17 comprising feeding to an infant which is susceptible to **necrotizing enterocolitis** a sufficient amount of an enteral formula containing: protein, carbohydrate and lipids, said lipids providing arachidonic acid and docosahexaenoic acid. . .

L15 ANSWER 11 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB Previous studies indicated that elevated tumour necrosis factor-alpha (**TNF**-.alpha.) levels may play a role in the development of **necrotizing enterocolitis** (NEC). The A(-308) and A(-238) variants of the promoter region of the **TNF**-.alpha. gene are reportedly associated with altered **TNF**-.alpha. production. The aim of our study was to determine the impact of these gene polymorphisms on the development and course of NEC in very-low-birthweight (VLBW) infants. Dried blood samples from 46 VLBW **neonates** with NEC were analysed using the method of restriction fragment length polymorphism. Samples from 90 VLBW **neonates** without NEC were used as controls. The prevalence of alleles with guanine-adenine transition in the -308 and -238 positions was the same in NEC and control subjects (12% vs 10% and 3% vs 4%, respectively). Conclusion: The investigated genetic variants of the **TNF**-.alpha. gene promoter region have no influence on the risk and course of NEC in VLBW infants.

ACCESSION NUMBER: 2001365977 EMBASE

TITLE: Genetic variants of the tumour necrosis factor-alpha promoter gene do not influence the development of **necrotizing enterocolitis**.

AUTHOR: Treszl A.; Kocsis I.; Szathmari M.; Schuler A.; Tulassay T.; Vasarhelyi B.

CORPORATE SOURCE: A. Treszl, Department of Pediatrics, Bokay u. 53, HU-1083 Budapest, Hungary. treand@freemail.hu

SOURCE: Acta Paediatrica, International Journal of Paediatrics, (2001) 90/10 (1182-1185).
Refs: 21
ISSN: 0803-5253 CODEN: APAEEL
COUNTRY: Norway
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
007 Pediatrics and Pediatric Surgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

TI Genetic variants of the tumour necrosis factor-alpha promoter gene do not influence the development of **necrotizing enterocolitis**
.

AB Previous studies indicated that elevated tumour necrosis factor-alpha (**TNF**-.alpha.) levels may play a role in the development of **necrotizing enterocolitis** (NEC). The A(-308) and A(-238) variants of the promoter region of the **TNF**-.alpha. gene are reportedly associated with altered **TNF**-.alpha. production. The aim of our study was to determine the impact of these gene polymorphisms on the development and course of NEC in very-low-birthweight (VLBW) infants. Dried blood samples from 46 VLBW **neonates** with NEC were analysed using the method of restriction fragment length polymorphism. Samples from 90 VLBW **neonates** without NEC were used as controls. The prevalence of alleles with guanine-adenine transition in the -308 and -238 positions was. . . in NEC and control subjects (12% vs 10% and 3% vs 4%, respectively). Conclusion: The investigated genetic variants of the **TNF**-.alpha. gene promoter region have no influence on the risk and course of NEC in VLBW infants.

CT Medical Descriptors:
*genetic variability
*promoter region
***necrotizing enterocolitis**
pathogenesis
genetic polymorphism
disease course
very low birth weight
blood sampling
gene frequency
risk factor
human
major clinical study
controlled study'
newborn
article
priority journal
***tumor necrosis factor alpha: EC, endogenous compound**

L15 ANSWER 12 OF 50 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 2

AB OBJECTIVE: We examd. the hypothesis that amniotic fluid (AF) infection and elevated cytokine concns. may cause neonatal injury beyond that expected solely from prematurity. METHODS: The effects of exposure to AF infection and elevated cytokine concns. were measured in 151 infants born to afebrile women in preterm labor with intact membranes at less than or equal to 34 wk' gestation. Amniotic fluid was collected by amniocentesis for culture and detn. of **tumor necrosis factor** -.alpha. and interleukin-6. Cytokine concns., stratified by AF infection,

were compared for three gestational age groups. We then examd. the assocns. between a pos. AF culture or elevated AF **tumor necrosis factor**-.alpha. concn. and adverse neonatal outcomes, adjusted for birth wt. RESULTS: Amniotic fluid from 45 (30%) of 151 pregnancies had microorganisms, an elevated **tumor necrosis factor**-.alpha. concn., or both. Amniotic fluid cytokine concns. were significantly higher among women in preterm labor at less than or equal to 30 wk, compared with 31-34 wk. Nine of 11 infants who died at less than or equal to 24 h of age had AF infection or elevated AF **tumor necrosis factor**-.alpha.. For the 140 surviving infants, AF infection and/or an elevated AF **tumor necrosis factor**-.alpha. was assocd. with respiratory distress syndrome (adjusted odds ratio [OR] 1.7), grade 3-4 intraventricular hemorrhage (adjusted OR 2.2), **necrotizing enterocolitis** (adjusted OR 1.8), and multiple organ dysfunction (adjusted OR 3.0). CONCLUSION: Among infants born at less than or equal to 34 wk to women who have intact membranes and are initially afebrile, those exposed to AF bacteria or cytokines have more adverse neonatal outcomes than unexposed infants of similar birth wt.

ACCESSION NUMBER: 2002:2019 CAPLUS
DOCUMENT NUMBER: 137:31896
TITLE: Amniotic fluid infection, cytokines, and adverse outcome among infants at 34 weeks' gestation or less
AUTHOR(S): Hitti, Jane; Tarczy-Hornoch, Peter; Murphy, Janet; Hillier, Sharon L.; Aura, Jan; Eschenbach, David A.
CORPORATE SOURCE: Department of Obstetrics and Gynecology and Pediatrics, University of Washington, Seattle, WA, USA
SOURCE: Obstetrics & Gynecology (New York, NY, United States) (2001), 98(6), 1080-1088
CODEN: OBGNAS; ISSN: 0029-7844
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB OBJECTIVE: We examd. the hypothesis that amniotic fluid (AF) infection and elevated cytokine concns. may cause neonatal injury beyond that expected solely from prematurity. METHODS: The effects of exposure to AF infection and elevated cytokine concns. were measured in 151 infants born to afebrile women in preterm labor with intact membranes at less than or equal to 34 wk' gestation. Amniotic fluid was collected by amniocentesis for culture and detn. of **tumor necrosis factor**-.alpha. and interleukin-6. Cytokine concns., stratified by AF infection, were compared for three gestational age groups. We then examd. the assocns. between a pos. AF culture or elevated AF **tumor necrosis factor**-.alpha. concn. and adverse neonatal outcomes, adjusted for birth wt. RESULTS: Amniotic fluid from 45 (30%) of 151 pregnancies had microorganisms, an elevated **tumor necrosis factor**-.alpha. concn., or both. Amniotic fluid cytokine concns. were significantly higher among women in preterm labor at

less than or equal to 30 wk, compared with 31-34 wk. Nine of 11 infants who died at less than or equal to 24 h of age had AF infection or elevated AF **tumor necrosis factor**-.alpha.. For the 140 surviving infants, AF infection and/or an elevated AF **tumor necrosis factor**-.alpha. was assocd. with respiratory distress syndrome (adjusted odds ratio [OR] 1.7), grade 3-4 intraventricular hemorrhage (adjusted OR 2.2), **necrotizing enterocolitis** (adjusted OR 1.8), and multiple organ dysfunction (adjusted OR 3.0). CONCLUSION: Among infants born at less than or equal to 34 wk to women who have intact membranes and are initially afebrile, those exposed to AF bacteria or cytokines have more adverse neonatal outcomes than unexposed infants of similar birth wt.

ST preterm **neonate** bacterial infection amniotic fluid **TNF**

IT Amniotic fluid
Death
Human
Multiple organ failure
Newborn
Pregnancy
Respiratory distress syndrome
(amniotic fluid infection, cytokines, and adverse outcome among infants at 34 wk' gestation or less)

IT **Tumor necrosis factors**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(amniotic fluid infection, cytokines, and adverse outcome among infants at 34 wk' gestation or less)

L15 ANSWER 13 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB The neuroadapted Kilham strain of the mumps virus produces lethal encephalitis in **newborn** hamsters after intracerebral inoculation. The pathogenesis of this encephalitis is not fully understood, but recently, apoptosis and associated cytokine production have been recognized to be major pathologic mechanisms by which viruses cause injury to neuronal host cells. To analyze the main factors producing brain injury in this viral encephalitis, the following questions were investigated: (1) does the virus induce neuronal apoptosis and (2) does expression of cytokines regulate the induction of neuronal apoptosis? Terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL) was used as a marker of neuronal apoptosis and TUNEL-positive neurons were widespread in the infected cerebral cortex. DNA fragmentation yielding DNA ladders characteristic of apoptosis was also observed in infected hamster brain tissue. Apoptotic cells in infected brains were observed after the appearance of inflammatory changes. Overexpression of IL-1.beta., but not **TNF**-.alpha. or Fas-L, was clearly detected in infected brains, as determined by Western blot and RT-PCR. Immunohistochemistry revealed a striking correlation between IL-1.beta. expression and neuronal apoptosis. Injection of recombinant IL-1.beta. into normal hamster brain resulted in neuronal apoptosis in cerebral cortex. On the other hand, neutralizing IL-1.beta. antibodies decreased the number of cells undergoing apoptosis in infected hamster brains and subsequent death. We conclude that the fatal encephalitis induced by the Kilham strain of the mumps virus is mediated by immunopathological processes and that overexpression of IL-1.beta., which mediates the induction of neuronal apoptosis, may play a major role in these processes.

ACCESSION NUMBER: 2001437978 EMBASE
TITLE: Neuronal apoptosis mediated by IL-1.beta. expression in viral encephalitis caused by a neuroadapted strain of the mumps virus (Kilham strain) in hamsters.
AUTHOR: Takikita S.; Takano T.; Narita T.; Takikita M.; Ohno M.; Shimada M.
CORPORATE SOURCE: S. Takikita, Department of Pediatrics, Shiga University of Medical Science, Tsukinowa, Seta, Otsu, Shiga 520-2192, Japan. takikita@belle.shiga-med.ac.jp
SOURCE: Experimental Neurology, (2001) 172/1 (47-59).
Refs: 40
ISSN: 0014-4886 CODEN: EXNEAC
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The neuroadapted Kilham strain of the mumps virus produces lethal encephalitis in **newborn** hamsters after intracerebral inoculation. The pathogenesis of this encephalitis is not fully understood, but recently, apoptosis and associated cytokine production.

. brain tissue. Apoptotic cells in infected brains were observed after the appearance of inflammatory changes. Overexpression of IL-1.beta., but not **TNF**-.alpha. or Fas-L, was clearly detected in infected brains, as determined by Western blot and RT-PCR. Immunohistochemistry revealed a striking correlation. . .
CT Medical Descriptors:
*apoptosis
***nerve cell necrosis**
*virus encephalitis: ET, etiology
*Mumps virus
virus strain
hamster
pathogenesis
brain injury
nick end labeling
brain cortex
gene overexpression
Western blotting
reverse transcription polymerase chain reaction
brain death
nonhuman
animal experiment
animal model
controlled study
animal tissue
animal cell
article
priority journal
*interleukin 1beta: EC, endogenous compound
DNA fragment
tumor necrosis factor alpha: EC, endogenous compound
FAS ligand: EC, endogenous compound
recombinant interleukin 1beta

AB Preconditioning brain with **tumor necrosis factor** alpha (**TNF**-.alpha.) can induce tolerance to experimental hypoxia and stroke and ceramide is a downstream messenger in the **TNF**-.alpha. signaling pathway. A hypoxic-ischemic (HI) insult in the immature rat injures brain primarily through apoptosis. Apoptosis is regulated by Bcl-2 family proteins. The authors explored whether ceramide protects against HI in the immature rat, and whether Bcl-2 family protein expression is involved. Hypoxia-ischemia was produced in seven-day-old rats by ligating the right carotid artery, followed by 2 hours of 8% oxygen exposure. Thirty minutes after HI, C(2)-ceramide (150 .mu.g/kg) was injected intraventricularly. Infarct volume was measured 5 days later. C(2)-ceramide reduced HI-induced brain damage by 45% to 65% compared with HI/dimethyl sulfoxide (DMSO) (vehicle control) or HI only groups. In separate experiments, brains of sham-operated control and HI only animals and animals subjected to HI plus C(2)-ceramide or DMSO infusion were sampled 6 hours, 24 hours, and 5 days after treatments and analyzed for Bcl-2, Bcl-xl, and Bax expression (Western blotting), and apoptosis (TUNEL assay). Augmented Bcl-2 and Bcl-xl levels in the C(2)-ceramide treated group were associated with a significant decrease in TUNEL-positive cells. The results support a protective role for ceramide in neonatal HI.

ACCESSION NUMBER: 2001012157 EMBASE
TITLE: The protective effect of ceramide in immature rat brain hypoxia-ischemia involves up-regulation of Bcl-2 and reduction of TUNEL-positive cells.
AUTHOR: Chen Y.; Ginis I.; Hallenbeck J.M.
CORPORATE SOURCE: Dr. J.M. Hallenbeck, Stroke Branch, Natl. Inst. Neurol. Disorders/Stroke, National Institutes of Health, 36 Convent Drive, Bethesda, MD 20892-4128, United States
SOURCE: Journal of Cerebral Blood Flow and Metabolism, (2001) 21/1 (34-40).
Refs: 35
ISSN: 0271-678X CODEN: JCBMDN
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Preconditioning brain with **tumor necrosis factor** alpha (**TNF**-.alpha.) can induce tolerance to experimental hypoxia and stroke and ceramide is a downstream messenger in the **TNF**-.alpha. signaling pathway. A hypoxic-ischemic (HI) insult in the immature rat injures brain primarily through apoptosis. Apoptosis is regulated by Bcl-2. . .
CT Medical Descriptors:
*brain protection
*nick end labeling
*brain hypoxia
*brain ischemia
receptor upregulation
stroke
apoptosis
protein expression
carotid artery ligation
brain infarction

Western blotting
correlation function
reperfusion
nonhuman
rat
animal experiment
animal model
controlled study
animal tissue
newborn
article
priority journal
*ceramide: EC, endogenous compound
*ceramide: CV, intracerebroventricular drug administration
*protein bcl 2: EC, endogenous compound
*protein bcl x: EC, endogenous compound
*protein Bax: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound
dimethyl sulfoxide

L15 ANSWER 15 OF 50 USPATFULL

AB Enteral formulas that contain long-chain polyunsaturated fatty acids (PUFAs), as arachidonic acid (AA) and docosahexaenoic acid (DHA) that are essentially free of cholesterol, are described. More particularly, the invention relates to methods for reducing the incidence of **necrotizing enterocolitis** by administering compositions which provide .omega.-6 and .omega.-3 long chain PUFAs, phospholipids and/or choline. Compositions from egg yolk lipids are presently preferred as they contain .omega.-6 and .omega.-3 long chain PUFAs and are predominantly in a phosphtidylcholine form. This is believed to provide a synergistic effect.

ACCESSION NUMBER: 2000:80795 USPATFULL
TITLE: Methods for reducing the incidence of **necrotizing enterocolitis**
INVENTOR(S): Carlson, Susan E., Kansas City, MO, United States
Ponder, Debra L., Evansville, IN, United States
Montalto, Michael B., Columbus, OH, United States
Dohnalek, Margaret H., Worthington, OH, United States
Benson, John D., Powell, OH, United States
Borror, David A., Westerville, OH, United States
Diodato, David V., Hilliard, OH, United States
PATENT ASSIGNEE(S): Abbott Laboratories, Abbott Park, IL, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6080787		20000627
APPLICATION INFO.:	US 1997-943576		19971003 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1997-804700, filed on 21 Feb 1997, now abandoned And a continuation-in-part of Ser. No. US 1997-825314, filed on 28 Mar 1997, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Spivack, Phyllis G.
LEGAL REPRESENTATIVE: Brainard, Thomas D.
NUMBER OF CLAIMS: 33
EXEMPLARY CLAIM: 1
LINE COUNT: 1066
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Methods for reducing the incidence of **necrotizing enterocolitis**

AB . . . that are essentially free of cholesterol, are described. More particularly, the invention relates to methods for reducing the incidence of **necrotizing enterocolitis** by administering compositions which provide .omega.-6 and .omega.-3 long chain PUFAs, phospholipids and/or choline. Compositions from egg yolk lipids are. . .

SUMM Some aspects of this invention were developed in the Neonatal Nursery of the University of Tennessee **Newborn** Center under the direction of Dr. Susan E. Carlson with financial support from the Ross Products Division of Abbott Laboratories. . .

SUMM **Necrotizing enterocolitis** (NEC) is a serious problem in infants having birth weights of less than about 1500 grams. Despite almost three (3). . .

SUMM Flageole et al., **Necrotizing Enterocolitis** of the **Newborn**, Review for the Clinician. Union-Med-Can. 1991 September-October; 120(5): 334-8, suggest the pathogenesis of NEC includes mesenteric ischemia, gastrointestinal immaturity, enteral. . .

SUMM Caplan et al., Role of Platelet Activating Factor and **Tumor Necrosis Factor**-Alpha in Neonatal **Necrotizing Enterocolitis**, Journal of Pediatrics, June, 1990, 960-964, report platelet activating factor and **tumor necrosis factor**-alpha are elevated in patients with NEC;

SUMM Kliegman et al., Clostridia as Pathogens in Neonatal **Necrotizing Enterocolitis**, The Journal of Pediatrics, August, 1979, 287-289, reports the isolation of Clostridia perfringens from children with neonatal NEC;

SUMM Ostertag et al., Early Enteral Feeding Does Not Affect the Incidence of **Necrotizing Enterocolitis**, Pediatrics, Vol. 77, No. 3, March 1986, 275-280, reports that dilute, early enteral calories do not adversely affect the incidence. . .

SUMM Bell et al., Neonatal **Necrotizing Enterocolitis**, Annals of Surgery, Vol. 187, January 1978, No. 1, 1-7, suggests the use of combination antimicrobial therapy for the treatment. . .

SUMM Eyal et al., **Necrotizing Enterocolitis** in the Very Low Birth Weight Infant: Expressed Breast Milk Feeding Compared with Parenteral Feeding, Archives of Disease in Childhood,. . .

SUMM Finer et al., Vitamin E and **Necrotizing Enterocolitis**, Pediatrics, Vol. 73, No. 3, March 1984 suggests that administration of vitamin E to reduce the incidence of severe sequelae. . .

SUMM Brown et al., Preventing **Necrotizing Enterocolitis** in **Neonates**, JAMA, Nov. 24, 1978, Vol. 240, No. 22, 2452-2454 reports that NEC can be virtually eliminated by the use of. . .

SUMM Kosloske, Pathogenesis and Prevention of **Necrotizing Enterocolitis**: A Hypothesis Based on Personal Observation and a Review of the Literature, Pediatrics, Vol. 74, No. 6, December 1984, 1086-1092,. . .

SUMM The present invention has many aspects. In a first aspect, the invention contemplates a method for reducing the incidence of **necrotizing enterocolitis** in an infant who is susceptible to **necrotizing enterocolitis**, said method comprising the administration of an effective amount of at least one long chain PUFA selected from the group. . .

SUMM Thus, in a further aspect, the invention provides a method for decreasing the incidence of **necrotizing enterocolitis**

in an infant, said method comprising feeding to said infant a sufficient
quantity of an enteral nutritional composition containing protein,. . .

SUMM In another aspect, the invention provides a method for decreasing the occurrence of **necrotizing enterocolitis** in a human infant, said method comprising administering to the infant phospholipids in an amount effective to reduce the incidence of **necrotizing enterocolitis**. Typically said phospholipids are administered to provide between about 60 and about 2400 .mu.moles, preferably between about 200 and about. . .

SUMM In yet another aspect, the invention provides a method for decreasing the occurrence of **necrotizing enterocolitis** in a human infant, said method comprising administering to the infant choline in an amount effective to reduce the incidence of **necrotizing enterocolitis**. Typically said choline is administered to provide between about 60 and about 1800 .mu.moles; more preferably between about 150 and. . .

SUMM More broadly, this aspect of the invention contemplates a method for reducing the incidence of **necrotizing enterocolitis** in an infant which is susceptible to **necrotizing enterocolitis**, said method comprising the administration of an effective amount of at least one long chain PUFA selected from the group. . .

SUMM There is further disclosed a method for decreasing the occurrence of **necrotizing enterocolitis** in a human infant, said method comprising administering to the infant egg phospholipids in an amount to result in at. . .

DETD . . . II and III were fed to infants in a study conducted in the Neonatal Nursery of the University of Tennessee **Newborn** Center under the direction of Dr. Susan E. Carlson with financial support from Ross Products Division of Abbott Laboratories (Study. . .

DETD Findings: An unanticipated finding was that a higher incidence of **necrotizing enterocolitis** (NEC) was seen in the Control Groups than the Experimental Group. Table VI groups the total number of **neonates** according to treatment (Control v. Experimental) and sets forth the number of **neonates** in each group that developed NEC. NEC was considered present or suspect when clinical signs and symptoms consistent with this. . .

CLM What is claimed is:

1. A method for reducing the incidence of **necrotizing enterocolitis** in an infant, said method comprising administering to an infant which is susceptible to **necrotizing enterocolitis** an effective amount of a nutritional composition containing protein, carbohydrate and phospholipids to provide at least 1.0 mg of .omega.-6. . .

13. The method according to claim 1 comprising feeding to an infant which is susceptible to **necrotizing enterocolitis** a sufficient amount of an enteral formula containing: protein, carbohydrate and phospholipids, said phospholipids providing arachidonic acid and docosahexaenoic acid. . .

14. A method for decreasing the incidence of **necrotizing enterocolitis** in an infant, said method comprising feeding to said infant a sufficient quantity of an enteral nutritional composition containing protein,. . .

21. A method for decreasing the incidence of **necrotizing**

enterocolitis in an infant, said method comprising administering to an infant susceptible to **necrotizing enterocolitis** a sufficient quantity of a nutritional composition containing protein, carbohydrates and phospholipids to provide between about 60 and about 2400. . .

27. A method for decreasing the incidence of **necrotizing enterocolitis** in an infant, said method comprising administering to an infant susceptible to **necrotizing enterocolitis** a sufficient quantity of a nutritional composition containing protein, carbohydrates and phospholipids to provide between about 60 and about 1800. . .

L15 ANSWER 16 OF 50 USPATFULL

AB The present invention provides purified and isolated polynucleotide sequences encoding human plasma platelet-activating factor acetylhydrolase. Also provided are materials and methods for the recombinant production of platelet-activating factor acetylhydrolase products which are expected to be useful in regulating pathological inflammatory events.

ACCESSION NUMBER: 2000:40639 USPATFULL
TITLE: Platelet-activating factor acetylhydrolase
INVENTOR(S): Cousens, Lawrence S., Oakland, CA, United States
Eberhardt, Christine D., Redmond, WA, United States
Gray, Patrick, Seattle, WA, United States
Trong, Hai Le, Edmonds, WA, United States
Tjoelker, Larry W., Kirkland, WA, United States
Wilder, Cheryl L., Seattle, WA, United States
PATENT ASSIGNEE(S): ICOS Corporation, Bothell, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6045794		20000404
APPLICATION INFO.:	US 1999-328474		19990609 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1997-910041, filed on 12 Aug 1997 which is a continuation-in-part of Ser. No. US 1995-483232, filed on 7 Jun 1995, now patented, Pat. No. US 5656431 which is a continuation-in-part of Ser. No. US 1994-318905, filed on 6 Oct 1994, now patented, Pat. No. US 5641669 which is a continuation-in-part of Ser. No. US 1993-113803, filed on 6 Oct 1993, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Prouty, Rebecca E.
ASSISTANT EXAMINER: Hutson, Richard
LEGAL REPRESENTATIVE: Marshall, O'Toole, Gerstein, Murray & Borun
NUMBER OF CLAIMS: 2
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 15 Drawing Figure(s); 13 Drawing Page(s)
LINE COUNT: 4346
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . Drug Dev. Res., 7: 361-375 (1986)], Crohn's disease [Denizot et al., Digestive Diseases and Sciences, 37(3): 432-437 (1992)], ischemic bowel necrosis/**necrotizing enterocolitis** [Denizot et al., supra and Caplan et al., Acta Paediatr., Suppl. 396: 11-17 (1994)], ulcerative colitis (Denizot et al., supra),. . .

SUMM . . . Example 16 herein; a rabbit model for arthritis is described in
Zarco et at., supra; rat models for ischemic bowel necrosis/ **necrotizing enterocolitis** are described in Furukawa et al., Ped. Res., 34,(2): 237-241 (1993) and Caplan et al., supra; a rabbit model for. . .
SUMM . . . Clin. Invest., 84: 1145-1146 (1989) (.alpha.-1-proteinase inhibitor); Debs et al., J. Immunol. , 140: 3482-3488 (1933) (recombinant gamma interferon and **tumor necrosis factor** alpha); Patent Cooperation Treaty (PCT) International Publication No. WO 94/20069 published Sep. 15, 1994 (recombinant pegylated granulocyte colony stimulating factor).
DETD . . . describe the in vivo therapeutic effect of administration of recombinant PAF-AH products of the invention on acute inflammation, pleurisy, asthma, **necrotizing enterocolitis**, adult respiratory distress syndrome and pancreatitis in animal models.
Example
20 describes the in vitro effect of recombinant PAF-AH product. . .
DETD A PAF-AH product of the invention was also tested in two different rat models for treatment of **necrotizing enterocolitis** (NEC), an acute hemorrhagic necrosis of the bowel which occurs in low birth weight infants and causes a significant morbidity. . .
DETD The efficacy of a PAF-AH product, rPH.2, was evaluated as follows in an NEC model in which **newborn** rats are stressed by formula feeding and asphyxia, two common risk factors for the disease in humans.
In this model,. . . 70-80% of the animals develop gross and microscopic intestinal injury similar to neonatal NEC by the third day of life. **Newborn** rats were obtained from pregnant Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, Ind.) that were anesthetized with CO.sub.2 and delivered via abdominal incision. **Newborn** animals were collected, dried, and maintained in a neonatal incubator during the entire experiment.
DETD First, separate groups of animals were used to assess the dosing and absorption characteristics of rPH.2. Normal **newborn** rat pups were given one of three different enteral or intraperitoneal doses of rPH.2 (3.lambda., 15.lambda., or 75.lambda.) at time. . .
DETD Following enteral dosing of rPH.2 in normal **newborn** rats, there was no measurable plasma PAF-AH activity at any time point using either the substrate incubation assay or the. . .
DETD In the NEC model, NEC was induced in **newborn** rats according to Caplan et al., Pediatr. Pathol., 14:1017-1028 (1994). Briefly, animals were fed with **newborn** puppy formula reconstituted from powder (Esbiliac, Borden Inc) every three hours via a feeding tube. The feeding
volume began at. . .
DETD . . . while intraperitoneal treatment at these doses had no demonstrable effect. These findings suggest that PAF-AH product supplementation for formula-fed premature **newborns** at risk for NEC may reduce the incidence of this disease.

L15 ANSWER 17 OF 50 USPATFULL
AB Enteral formulas that contain long-chain polyunsaturated fatty acids (PUFAs) and a process for making such enteral compositions are described. More particularly, the invention relates to enteral compositions which provide long chain PUFAs arachidonic acid (AA) and docosahexaenoic acid (DHA) essentially free of cholesterol and may be derived from egg yolk lipids, and thus are predominantly in a phospholipid form. The process of making such a composition provides improved organoleptic and stability properties. Enteral compositions

according to this invention may be used to feed infants, particularly pre-term infants, to promote neural development and development of visual acuity, and to reduce the incidence of **necrotizing enterocolitis**.

ACCESSION NUMBER:	2000:31066 USPATFULL
TITLE:	Process of making an enteral formula containing long-chain polyunsaturated fatty acids
INVENTOR(S):	Borror, David A., Westerville, OH, United States Diodato, David V., Hilliard, OH, United States Ponder, Debra L., Morristown, NJ, United States Dohnalek, Margaret H., Worthington, OH, United States
PATENT ASSIGNEE(S):	Abbott Laboratories, Abbott Park, IL, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6036992		20000314
APPLICATION INFO.:	US 1999-270423		19990316 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1997-825314, filed on 28 Mar 1997, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Weier, Anthony J.		
LEGAL REPRESENTATIVE:	Brainard, Thomas D.		
NUMBER OF CLAIMS:	18		
EXEMPLARY CLAIM:	1		
LINE COUNT:	832		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . feed infants, particularly pre-term infants, to promote neural development and development of visual acuity, and to reduce the incidence of **necrotizing enterocolitis**.

SUMM **Necrotizing enterocolitis** (NEC) is a serious problem in infants having birth weights of less than about 1500 grams. Despite almost three (3). . .

SUMM Flageole et al., **Necrotizing Enterocolitis** of the **Newborn**, Review for the Clinician. Union-Med-Can. 1991 September-October; 120(5): 334-8, suggest the pathogenesis of NEC includes mesenteric ischemia, gastrointestinal immaturity, enteral. . .

SUMM Caplan et al., Role of Platelet Activating Factor and **Tumor Necrosis Factor**-Alpha in Neonatal **Necrotizing Enterocolitis**, Journal of Pediatrics, Jun., 1990, 960-964, report platelet activating factor and **tumor necrosis factor**-alpha are elevated in patients with NEC;

SUMM Kliegman et al., Clostridia as Pathogens in Neonatal **Necrotizing Enterocolitis**, The Journal of Pediatrics, August, 1979, 287-289, reports the isolation of Clostridia perfringens from children with neonatal NEC;

SUMM Ostertag et al., Early Enteral Feeding Does Not Affect the Incidence of **Necrotizing Enterocolitis**, Pediatrics, Vol. 77, No. 3, March 1986, 275-280, reports that dilute, early enteral calories do not adversely affect the incidence. . .

SUMM Bell et al., Neonatal **Necrotizing Enterocolitis**, Annals of Surgery, Vol. 187, January 1978, No. 1, 1-7, suggests the use of combination antimicrobial therapy for the treatment. . .

SUMM Eyal et al., **Necrotizing Enterocolitis** in the Very Low Birth Weight Infant: Expressed Breast Milk Feeding Compared with Parenteral Feeding, Archives of Disease in Childhood,. . .

SUMM Finer et al., Vitamin E and **Necrotizing Enterocolitis**, Pediatrics, Vol. 73, No. 3, March 1984 suggests that administration of

vitamin E to reduce the incidence of severe sequelae. . .

SUMM Brown et al., Preventing **Necrotizing Enterocolitis** in **Neonates**, JAMA, Nov. 24, 1978, Vol. 240, No. 22, 2452-2454 reports that NEC can be virtually eliminated by the use of. . .

SUMM Kosloske, Pathogenesis and Prevention of **Necrotizing Enterocolitis**: A Hypothesis Based on Personal Observation and a Review of the Literature, Pediatrics, Vol. 74, No. 6, December 1984, 1086-1092,. . .

SUMM More broadly, this aspect of the invention contemplates a method for reducing the incidence of **necrotizing enterocolitis** in an infant which is susceptible to **necrotizing enterocolitis**, said method comprising the administration of an effective amount of at least one long chain PUFA selected from the group. . .

SUMM There is further disclosed a method for dedreasing the occurrence of **necrotizing enterocolitis** in a human infant, said method comprising administering to the infant egg phospholipids in an amount to result in at. . .

DETD . . . II and III were fed to infants in a study conducted in the Neonatal Nursery of the University of Tennessee **Newborn** Center under the direction of Dr. Susan E. Carlson with financial support from Ross Products Division of Abbott Laboratories (Study. . .

DETD Findings: A surprising finding was that there appeared to be a higher incidence of **necrotizing enterocolitis** (NEC) in one of the randomized groups. The blind was broken early to determine if the Experimental Formula was causing. . .

DETD Table VI groups the total number of **neonates** according to treatment (Control v. Experimental) and sets forth the number of **neonates** in each group that developed NEC. NEC was considered present or suspect when clinical signs and symptoms consistent with this. . .

L15 ANSWER 18 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB The names of the hematopoietic cytokines are misleading because in addition to their effects on bone marrow and bone marrow-derived cells, they have many diverse effects, including effects on the gastrointestinal tract. These effects may be directly mediated by interaction with specific receptors on gastrointestinal epithelial cells, or they may result from their effects on circulating or bowel wall leukocytes and the cytokines these cells produce. As might be expected of factors largely defined by their effects on inflammatory cells, the hematopoietic cytokines are intimately involved in the processes of bowel injury. Further investigations are needed to define the role of hematopoietic cytokines in the human **neonate**'s balance between local gastrointestinal host defense and bowel wall injury. This could lead to effective strategies for the treatment and prevention of NEC.

ACCESSION NUMBER: 2000305415 EMBASE

TITLE: **Necrotizing enterocolitis** and hematopoietic cytokines.

AUTHOR: Ledbetter D.J.; Juul S.E.

CORPORATE SOURCE: Dr. D.J. Ledbetter, Division of Pediatric Surgery, Department of Surgery, JHMHC, PO Box 100286, Gainesville, FL 32610-0286, United States. Ledbedj@mail.surgery.ufl.edu

SOURCE: Clinics in Perinatology, (2000) 27/3 (697-716).
Refs: 134
ISSN: 0095-5108 CODEN: CLPEDL

COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
TI **Necrotizing enterocolitis** and hematopoietic cytokines.
AB . . . in the processes of bowel injury. Further investigations are needed to define the role of hematopoietic cytokines in the human **neonate**'s balance between local gastrointestinal host defense and bowel wall injury. This could lead to effective strategies for the treatment and. . .
CT Medical Descriptors:
***necrotizing enterocolitis: DT, drug therapy**
***necrotizing enterocolitis: EP, epidemiology**
***necrotizing enterocolitis: ET, etiology**
***necrotizing enterocolitis: SU, surgery**
***necrotizing enterocolitis: TH, therapy**
clinical feature
disease course
parenteral nutrition
decompression
prematurity
risk factor
human
nonhuman
review
priority journal
*cytokine: EC, endogenous compound
cytokine receptor: EC, endogenous compound
nitric oxide: EC, endogenous compound
granulocyte macrophage colony stimulating factor: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound
transforming growth factor beta: EC, endogenous compound
antibiotic agent: DT, drug therapy
hemopoietic growth factor: EC, endogenous. . .

L15 ANSWER 19 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AB This review is a short synopsis of the roles cytokines play during fetal life, initiation of labor, and in neonatal immunity and diseases. Hematopoietic growth factors regulate the maturation of progenitors in fetal and neonatal hematopoietic organs. Cytokines act as extra-hematopoietic growth factors, modulators of feto-maternal tolerance and are involved in selective apoptosis during tissue remodeling. Inter-regulation of cytokine networks is critical for normal function and maturation of neonatal host defenses. Antigen specific immunity develops later in life and **neonates** initially depend on natural (innate) immunity. Cytokines regulate innate immunity and connect it with antigen specific adaptive immunity. Some cytokines have already found a place in routine NICU therapy (EPO and G-CSF), while diagnostic and therapeutic uses of others are under investigation (TPO, **TNF**-.alpha., etc.).
ACCESSION NUMBER: 2001014840 EMBASE
TITLE: Cytokines and **neonates**.
AUTHOR: Nesin M.; Cunningham-Rundles S.
CORPORATE SOURCE: Dr. M. Nesin, Department of Pediatrics, Weill Med. Coll. of
Cornell Univ., 525 East 68th Street, New York, NY 10021, United States. mnesin@mail.med.cornell.edu

SOURCE: American Journal of Perinatology, (2000) 17/8 (393-404).
Refs: 61
ISSN: 0735-1631 CODEN: AJPEEK
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
TI Cytokines and **neonates**.
AB . . . networks is critical for normal function and maturation of neonatal host defenses. Antigen specific immunity develops later in life and **neonates** initially depend on natural (innate) immunity. Cytokines regulate innate immunity and connect it with antigen specific adaptive immunity. Some cytokines. . . a place in routine NICU therapy (EPO and G-CSF), while diagnostic and therapeutic uses of others are under investigation (TPO, **TNF**-.alpha., etc.).
CT Medical Descriptors:
*immunity
hematopoiesis
apoptosis
immunological tolerance
premature labor
newborn sepsis
necrotizing enterocolitis: DT, drug therapy
newborn intensive care
hemolytic anemia: DT, drug therapy
inflammation
human
newborn
review
priority journal
*cytokine: CB, drug combination
*cytokine: DT, drug therapy
gamma interferon: EC, endogenous compound
immunoglobulin: EC, endogenous compound
lymphotoxin: EC, endogenous compound
interleukin 2: EC,. . . therapy
interleukin 15: EC, endogenous compound
alpha interferon: EC, endogenous compound
beta interferon: EC, endogenous compound
interleukin 1: EC, endogenous compound
interleukin 6: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound
RANTES: EC, endogenous compound
interleukin 8: EC, endogenous compound
interleukin 16: EC, endogenous compound
unindexed drug

L15 ANSWER 20 OF 50 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 3
AB Previous investigators have relied on administration of pro-inflammatory cytokines or invasive surgical procedures to reproduce the morphol. changes of **necrotizing enterocolitis** (NEC) in rats. However, these artificial insults do not mimic the human disease. We developed a reproducible model of NEC in rats that more closely resembles human NEC and detd. the pattern of inflammatory cytokine expression in this model. **Newborn** rats were randomized into four groups. Groups 1 and 2 were breast-fed, while Groups 3 and 4 were gavaged with

formula thrice daily. In addn., Groups 2 and 4 were subjected to 3 min of hypoxia thrice daily, prior to each feeding. The rats were killed on day 4 and the distal 2 cm of terminal ileum was harvested for morphol. studies and anal. of inflammatory cytokine mRNA expression. Nearly 70% of formula-fed neonatal rats displayed moderate or severe morphol. abnormalities resembling human NEC. Breast-fed pups had normal histol. The terminal ileum from rats with abnormal histol. demonstrated increased inducible nitric oxide synthase (iNOS) expression, decreased interleukin-12 (IL-12) mRNA expression, and enterocyte apoptosis. There was a trend toward upregulation of IFN-.gamma. mRNA, but no difference in expression of **TNF**-.alpha. mRNA. Hypoxia did not significantly alter intestinal morphol. or mRNA expression. Formula-fed neonatal rats, with or without hypoxia, exhibit morphol. changes in the intestinal epithelium similar to those seen in patients with acute NEC. The mechanism likely involves upregulation of iNOS mRNA, enterocyte apoptosis, and decreased IL-12 prodn. in the intestinal epithelium. This model may offer a simple reproducible method for inducing exptl. NEC. (c) 2000 Academic Press.

ACCESSION NUMBER: 2000:413280 CAPLUS
DOCUMENT NUMBER: 134:3400
TITLE: Expression of Inducible Nitric Oxide Synthase and Interleukin-12 in Experimental **Necrotizing Enterocolitis**
AUTHOR(S): Nadler, Evan P.; Dickinson, Eva; Knisely, Alex; Zhang, Xiao-Ru; Boyle, Patricia; Beer-Stolz, Donna; Watkins, Simon C.; Ford, Henri R.
CORPORATE SOURCE: Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, 15213, USA
SOURCE: Journal of Surgical Research (2000), 92(1), 71-77
CODEN: JSGRA2; ISSN: 0022-4804
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
TI Expression of Inducible Nitric Oxide Synthase and Interleukin-12 in Experimental **Necrotizing Enterocolitis**
AB Previous investigators have relied on administration of pro-inflammatory cytokines or invasive surgical procedures to reproduce the morphol. changes of **necrotizing enterocolitis** (NEC) in rats. However, these artificial insults do not mimic the human disease. We developed a reproducible model of NEC in rats that more closely resembles human NEC and detd. the pattern of inflammatory cytokine expression in this model. **Newborn** rats were randomized into four groups. Groups 1 and 2 were breast-fed, while Groups 3 and 4 were gavaged with formula thrice daily. In addn., Groups 2 and 4 were subjected to 3 min of hypoxia thrice daily, prior to each feeding. The rats were killed on day 4 and the distal 2 cm of terminal ileum was harvested for morphol. studies and anal. of inflammatory cytokine mRNA expression. Nearly 70% of formula-fed neonatal rats displayed moderate or severe morphol. abnormalities resembling human NEC. Breast-fed pups had normal histol.

The terminal ileum from rats with abnormal histol. demonstrated increased inducible nitric oxide synthase (iNOS) expression, decreased interleukin-12 (IL-12) mRNA expression, and enterocyte apoptosis. There was a trend toward upregulation of IFN-.gamma. mRNA, but no difference in expression of **TNF**-.alpha. mRNA. Hypoxia did not significantly alter intestinal morphol. or mRNA expression. Formula-fed neonatal rats, with or without hypoxia, exhibit morphol. changes in the intestinal epithelium similar to those seen in patients with acute NEC. The mechanism likely involves upregulation of iNOS mRNA, enterocyte apoptosis, and decreased IL-12 prodn. in the intestinal epithelium. This model may offer a simple reproducible method for inducing exptl. NEC. (c) 2000 Academic Press.

ST NO synthase interleukin 12 **necrotizing enterocolitis**

IT Apoptosis
(enterocyte; gene expression of inducible nitric oxide synthase and pro-inflammatory cytokines in exptl. **necrotizing enterocolitis**)

IT Hypoxia, animal
Newborn
(gene expression of inducible nitric oxide synthase and pro-inflammatory cytokines in exptl. **necrotizing enterocolitis**)

IT mRNA
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(gene expression of inducible nitric oxide synthase and pro-inflammatory cytokines in exptl. **necrotizing enterocolitis**)

IT Interleukin 12
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene expression of inducible nitric oxide synthase and pro-inflammatory cytokines in exptl. **necrotizing enterocolitis**)

IT Intestine
(ileum; gene expression of inducible nitric oxide synthase and pro-inflammatory cytokines in exptl. **necrotizing enterocolitis**)

IT Intestine, disease
(pseudomembranous enterocolitis; gene expression of inducible nitric oxide synthase and pro-inflammatory cytokines in exptl. **necrotizing enterocolitis**)

IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.gamma.; gene expression of inducible nitric oxide synthase and pro-inflammatory cytokines in exptl. **necrotizing enterocolitis**)

IT 125978-95-2, Nitric oxide synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene expression of inducible nitric oxide synthase and pro-inflammatory cytokines in exptl. **necrotizing enterocolitis**)

L15 ANSWER 21 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB We examined the effect of prenatal alcohol exposure (PAE) on **tumor necrosis factor**-.alpha.-(**TNF**.alpha.) induced cell death in primary astrocyte cultures. Flow cytometry revealed that PAE increased the sensitivity of astrocytes to the cytotoxic effects of

TNF.alpha. when compared to astrocytes prepared from pair-fed and chow-fed controls. In a number of cell types, **TNF**.alpha. regulates cell growth or death, in part, by the hydrolysis of sphingomyelin to ceramide and sphingosine-1-phosphate (SPP). Using a 3-(4.5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cytotoxic assay we found that PAE increased the sensitivity of astrocytes to the cytotoxic effects of **TNF**.alpha., sphingomyelinase (SMase), and C2- and C6-ceramide. The increasing cellular concentrations of SPP, a sphingolipid metabolic that induces cell growth, protected the cells from **TNF**.alpha.-induced cell death. N,N-dimethylsphingosine (DMS), which inhibits SPP production, and N-oleoylethanolamine, which inhibits acid ceramidases, increased **TNF**.alpha.-induced cytotoxicity in astrocytes prepared from PAE rats. These studies suggest that PAE shifts the balance of sphingolipid metabolism in favor of a pathway that increases the susceptibility of astrocytes to the cytotoxic effect of **TNF**.alpha.. (C) 2000 Elsevier Science Inc.

ACCESSION NUMBER: 2000288690 EMBASE
TITLE: Prenatal alcohol exposure increases **TNF**.alpha.-induced cytotoxicity in primary astrocytes.
AUTHOR: De Vito W.J.; Xhaja K.; Stone S.
CORPORATE SOURCE: W.J. De Vito, Division of Endocrinology, Univ. of Massachusetts Med. Center, 55 Lake Avenue North, Worcester, MA 01655, United States. william.devito@umassmed.edu
SOURCE: Alcohol, (2000) 21/1 (63-71).
Refs: 58
ISSN: 0741-8329 CODEN: ALCOEX
PUBLISHER IDENT.: S 0741-8329(00)00078-1
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
008 Neurology and Neurosurgery
040 Drug Dependence, Alcohol Abuse and Alcoholism
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English

TI Prenatal alcohol exposure increases **TNF**.alpha.-induced cytotoxicity in primary astrocytes.

AB We examined the effect of prenatal alcohol exposure (PAE) on **tumor necrosis factor**-.alpha.-(**TNF**.alpha.) induced cell death in primary astrocyte cultures. Flow cytometry revealed that PAE increased the sensitivity of astrocytes to the cytotoxic effects of **TNF**.alpha. when compared to astrocytes prepared from pair-fed and chow-fed controls. In a number of cell types, **TNF**.alpha. regulates cell growth or death, in part, by the hydrolysis of sphingomyelin to ceramide and sphingosine-1-phosphate (SPP). Using a 3-(4.5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cytotoxic assay we found that PAE increased the sensitivity of astrocytes to the cytotoxic effects of **TNF**.alpha., sphingomyelinase (SMase), and C2- and C6-ceramide. The increasing cellular concentrations of SPP, a sphingolipid metabolic that induces cell growth, protected the cells from **TNF**.alpha.-induced cell death. N,N-dimethylsphingosine (DMS), which inhibits SPP production, and N-oleoylethanolamine, which inhibits acid ceramidases, increased **TNF**.alpha.-induced cytotoxicity in astrocytes prepared from PAE rats. These studies suggest that PAE shifts the balance of sphingolipid metabolism in favor of a pathway that increases the susceptibility of astrocytes to the cytotoxic effect of **TNF**.alpha.. (C) 2000

Elsevier Science Inc.
CT Medical Descriptors:
*prenatal drug exposure
*astrocyte
*cytotoxicity
flow cytometry
nerve cell necrosis: ET, etiology
cell growth
chemosensitivity
cell protection
DNA content
nonhuman
rat
controlled study
animal cell
newborn
article
*alcohol: TO, drug toxicity
***tumor necrosis factor alpha**
sphingomyelin
ceramide
sphingosine 1 phosphate
sphingomyelin phosphodiesterase
ethanolamine derivative
acylsphingosine deacylase

L15 ANSWER 22 OF 50 USPATFULL

AB The present invention provides purified and isolated polynucleotide sequences encoding human plasma platelet-activating factor acetylhydrolase. Also provided are materials and methods for the recombinant production of platelet-activating factor acetylhydrolase products which are expected to be useful in regulating pathological inflammatory events.

ACCESSION NUMBER: 1999:137456 USPATFULL
TITLE: Platelet-activating factor acetylhydrolase
INVENTOR(S): Cousens, Lawrence S., Oakland, CA, United States
Eberhardt, Christine D., Redmond, WA, United States
Gray, Patrick, Seattle, WA, United States
Trong, Hai Le, Edmonds, WA, United States
Tjoelker, Larry W., Kirkland, WA, United States
Wilder, Cheryl L., Seattle, WA, United States
PATENT ASSIGNEE(S): ICOS Corporation, Bothell, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5977308		19991102
APPLICATION INFO.:	US 1997-910041		19970812 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1995-483232, filed on 7 Jun 1995, now patented, Pat. No. US 5656431 which is a continuation-in-part of Ser. No. US 1994-318905, filed on 6 Oct 1994, now patented, Pat. No. US 5641669 which is a continuation-in-part of Ser. No. US 1993-133803, filed on 6 Oct 1993, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Elliott, George C.
ASSISTANT EXAMINER: McGarry, Sean
LEGAL REPRESENTATIVE: Marshall, O'Toole, Gerstein, Murray & Borun
NUMBER OF CLAIMS: 9

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 15 Drawing Figure(s); 13 Drawing Page(s)
LINE COUNT: 4530
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . Drug Dev. Res., 7: 361-375 (1986)], Crohn's disease [Denizot et
al., Digestive Diseases and Sciences, 37(3): 432-437 (1992)], ischemic
bowel necrosis/**necrotizing enterocolitis** [Denizot et
al., supra and Caplan et al., Acta Paediatr., Suppl. 396: 11-17 (1994)],
ulcerative colitis (Denizot et al., supra),. . .
SUMM . . . Example 16 herein; a rabbit model for arthritis is described in
Zarco et at., supra; rat models for ischemic bowel necrosis/
necrotizing enterocolitis are described in Furukawa et
al., Ped. Res., 34,(2): 237-241 (1993) and Caplan et al., supra; a
rabbit model for. . .
SUMM . . . J. Clin. Invest., 84: 1145-1146 (1989) (.alpha.-1-proteinase
inhibitor); Debs et al., J. Immunol., 140: 3482-3488 (1933) (recombinant
gamma interferon and **tumor necrosis factor**
alpha); Patent Cooperation Treaty (PCT) International Publication No. WO
94/20069 published Sep. 15, 1994 (recombinant pegylated granulocyte
colony stimulating factor).
DETD . . . describe the in vivo therapeutic effect of administration of
recombinant PAF-AH products of the invention on acute inflammation,
pleurisy, asthma, **necrotizing enterocolitis**, adult
respiratory distress syndrome and pancreatitis in animal models. Example
20 describes the in vitro effect of recombinant PAF-AH product. . .
DETD A PAF-AH product of the invention was also tested in two different rat
models for treatment of **necrotizing enterocolitis**
(NEC), an acute hemorrhagic necrosis of the bowel which occurs in low
birth weight infants and causes a significant morbidity. . .
DETD The efficacy of a PAF-AH product, rPH.2, was evaluated as follows in an
NEC model in which **newborn** rats are stressed by formula
feeding and asphyxia, two common risk factors for the disease in humans.
In this model,. . . 70-80% of the animals develop gross and
microscopic intestinal injury similar to neonatal NEC by the third day
of life. **Newborn** rats were obtained from pregnant
Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, Ind.) that
were anesthetized with CO.sub.2 and delivered via abdominal incision.
Newborn animals were collected, dried, and maintained in a
neonatal incubator during the entire experiment.
DETD First, separate groups of animals were used to assess the dosing and
absorption characteristics of rPH.2. Normal **newborn** rat pups
were given one of three different enteral or intraperitoneal doses of
rPH.2 (3.lambda., 15.lambda., or 75.lambda.) at time. . .
DETD Following enteral dosing of rPH.2 in normal **newborn** rats,
there was no measurable plasma PAF-AH activity at any time point using
either the substrate incubation assay or the. . .
DETD In the NEC model, NEC was induced in **newborn** rats according to
Caplan et al., Pediatr. Pathol., 14:1017-1028 (1994). Briefly, animals
were fed with **newborn** puppy formula reconstituted from powder
(Esbiliac, Borden Inc) every three hours via a feeding tube. The feeding
volume began at. . .
DETD . . . while intraperitoneal treatment at these doses had no

demonstrable effect. These findings suggest that PAF-AH product supplementation for formula-fed premature **newborns** at risk for NEC may reduce the incidence of this disease.

L15 ANSWER 23 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB Objective: To evaluate the influence of the methylxanthine derivative, pentoxifylline, on plasma levels of **tumor necrosis factor** (**TNF**)-.alpha., interleukin (IL1)-1, and IL-6 in prematurely delivered infants with generalized bacterial infections and to assess the effect of this immunomodulating drug on the clinical outcome in **newborns** with sepsis. Design: A prospective, randomized, double-blind trial. Setting: The neonatal intensive therapy units in university teaching hospitals. Patients: One hundred patients with sepsis admitted during a 1.5-yr period. Interventions: Patients were randomly assigned to receive pentoxifylline (pentoxifylline group) in a dose of 5 mg/kg/hr for 6 hrs on 6 successive days or an identically presented placebo (placebo group). Measurements and Main Results: Only infants with sepsis confirmed by positive blood culture were recruited into the study. There were no significant differences at randomization between the pentoxifylline and placebo groups with regard to the birth weight, gestational age, gender, Apgar score, hypotension, neutropenia, thrombocytopenia, metabolic acidosis, plasma levels of cytokines, and occurrence of shock. Plasma levels of **TNF**, IL-1, and IL-6 were evaluated before and after the drug or placebo administration on the first, third, and sixth days of therapy. Cytokines were determined by immunoenzymetric test EASIA (**TNF**) and Endogen Interleukin-Elisa (IL-1, IL-6). The frequency of Gram-negative sepsis was similar in both groups (37.5% and 36.8%). Pentoxifylline significantly diminished plasma **TNF** levels (p = .009) but had no effect on plasma IL-1 levels. Mean plasma IL-6 levels, which were measured in the pentoxifylline group on the 6th day of the study, were significantly lower compared with respective data obtained in the placebo group. Only 1 of 40 infants with sepsis in the pentoxifylline group died, whereas 6 of 38 infants in the placebo group did not survive (p = .046). An increased incidence of disordered peripheral circulation and metabolic acidosis (p = .048), anuria or oliguria (p = .03), disseminated intravascular coagulation (p = .043), and the occurrence of clinical symptoms of **necrotizing enterocolitis** (p = .025) was observed in the course of sepsis in infants in the placebo group. Conclusion: Pentoxifylline significantly affects the synthesis of **TNF** and IL-6 as well as reduces the mortality rate in premature infants with sepsis. The dosage and schedule of drug administration in this study attenuated the severity of the clinical course of sepsis in this group of patients.

ACCESSION NUMBER: 1999165154 EMBASE

TITLE: Effect of the immunomodulating agent, pentoxifylline, in the treatment of sepsis in prematurely delivered infants: A placebo-controlled, double- blind trial.

AUTHOR: Lauterbach R.; Pawlik D.; Kowalczyk D.; Ksycinski W.; Helwich E.; Zembala M.

CORPORATE SOURCE: Dr. R. Lauterbach, Department of Neonatology, Jagiellonian Univ. Medical College, Kopernika 23, P-31-501 Cracow, Poland

SOURCE: Critical Care Medicine, (1999) 27/4 (807-814).
Refs: 28
ISSN: 0090-3493 CODEN: CCMDC7

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
024 Anesthesiology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Objective: To evaluate the influence of the methylxanthine derivative, pentoxifylline, on plasma levels of **tumor necrosis factor** (**TNF**)-.alpha., interleukin (IL1)-1, and IL-6 in prematurely delivered infants with generalized bacterial infections and to assess the effect of this immunomodulating drug on the clinical outcome in **newborns** with sepsis. Design: A prospective, randomized, double-blind trial. Setting: The neonatal intensive therapy units in university teaching hospitals. Patients: One. . . age, gender, Apgar score, hypotension, neutropenia, thrombocytopenia, metabolic acidosis, plasma levels of cytokines, and occurrence of shock. Plasma levels of **TNF**, IL-1, and IL-6 were evaluated before and after the drug or placebo administration on the first, third, and sixth days of therapy. Cytokines were determined by immunoenzymetric test EASIA (**TNF**) and Endogen Interleukin-Elisa (IL-1, IL-6). The frequency of Gram-negative sepsis was similar in both groups (37.5% and 36.8%). Pentoxifylline significantly diminished plasma **TNF** levels (p = .009) but had no effect on plasma IL-1 levels. Mean plasma IL-6 levels, which were measured in. . . .048), anuria or oliguria (p = .03), disseminated intravascular coagulation (p = .043), and the occurrence of clinical symptoms of **necrotizing enterocolitis** (p = .025) was observed in the course of sepsis in infants in the placebo group. Conclusion: Pentoxifylline significantly affects the synthesis of **TNF** and IL-6 as well as reduces the mortality rate in premature infants with sepsis. The dosage and schedule of drug. . .

CT Medical Descriptors:
*immunomodulation
*sepsis: DT, drug therapy
prematurity
treatment outcome
newborn intensive care
dose response
blood level
cytokine production
mortality
metabolic acidosis: CO, complication
anuria: CO, complication
oliguria: CO, complication
disseminated intravascular clotting: CO, complication
necrotizing enterocolitis: CO, complication
septic shock: CO, complication
clinical feature
serology
disease course
human
male
female
major clinical study
clinical trial

randomized controlled trial
double blind procedure
controlled study
intravenous drug administration
article
priority journal
*immunomodulating. . . CT, clinical trial
*pentoxifylline: CB, drug combination
*pentoxifylline: DT, drug therapy
*methylxanthine derivative: CT, clinical trial
*methylxanthine derivative: CB, drug combination
*methylxanthine derivative: DT, drug therapy
placebo
tumor necrosis factor: EC, endogenous compound
interleukin 1: EC, endogenous compound
interleukin 6: EC, endogenous compound
cytokine: EC, endogenous compound
amoxicillin plus clavulanic acid: CB,. . .

L15 ANSWER 24 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AB Results of genetic association studies in UC are conflicting. We propose that the power of candidate gene studies will increase when disease heterogeneity is taken into account. Phenotype frequencies of molecularly defined HLA-DR alleles, polymorphisms in the tumour necrosis factor-alpha (**TNF**-.alpha.), lymphotoxin-alpha (LT-.alpha.), IL-1 receptor antagonist (IL-1Ra) and IL-1.beta. genes were determined in 98 clinically well characterized UC patients with a mean period of follow up of 10 years, and ethnically matched healthy controls (HC). The alleles HLA-DRB1*0103 (phenotype frequency 6% versus 0- 2%; P = 0.0002; odds ratio (OR) 27.6) and DRB1*15 (41% versus 26%; P = 0.001; OR = 2.0, compared with HC) were associated with overall disease susceptibility. Subgroup analysis revealed that DRB1*15 was only increased in females (53% versus 24%; P < 0.0001; OR = 3.5), but not in males. With regard to disease localization, all DRB1*0103+ patients had extensive disease (P<0.002; OR= 33.5), and DRB1*15 was found in 59% of females with extensive colitis (P < 0.0001; OR = 4.4). DRBI*0103 was significantly increased in patients undergoing colectomy (P<0.0002; OR=84). No association between overall disease susceptibility and the cytokine gene polymorphisms were found. Subgroup analysis revealed several significant associations, but most did not retain significance when corrected for multiple comparisons. However, a noticeable finding was that haplotype **TNF**-C was significantly associated with progression in extent of disease (P = 0.003, OR = 20.4). This study provides additional evidence for the role of DRB1 alleles in the susceptibility to UC, and supports the hypothesis that these alleles may determine the severity of the disease. The cytokine gene polymorphisms evaluated in this study do not seem to be strong risk factors for the overall disease susceptibility in UC, but may be involved in determining the severity of the disease.
ACCESSION NUMBER: 1999040365 EMBASE
TITLE: Genetic markers in clinically well defined patients with ulcerative colitis (UC).
AUTHOR: Bouma G.; Crusius J.B.A.; Garcia-Gonzalez M.A.; Meijer B.U.G.A.; Hellemans H.P.R.; Hakvoort R.J.; Schreuder G.M.Th.; Kostense P.J.; Meuwissen S.G.M.; Pena A.S.
CORPORATE SOURCE: Dr. A.S. Pena, Lab. Gastrointestinal Immunogenetics, Fac.

of Medicine Vrije Universiteit, Van der Boechorststraat 7, 1081 BT Amsterdam, Netherlands
SOURCE: Clinical and Experimental Immunology, (1999) 115/2 (294-300).
Refs: 44
ISSN: 0009-9104 CODEN: CEXIAL
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
026 Immunology, Serology and Transplantation
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB . . . when disease heterogeneity is taken into account. Phenotype frequencies of molecularly defined HLA-DR alleles, polymorphisms in the tumour necrosis factor-alpha (**TNF**-.alpha.), lymphotoxin-alpha (LT-.alpha.), IL-1 receptor antagonist (IL-1Ra) and IL-1.beta. genes were determined in 98 clinically well characterized UC patients with a. . . significant associations, but most did not retain significance when corrected for multiple comparisons. However, a noticeable finding was that haplotype **TNF**-C was significantly associated with progression in extent of disease (P = 0.003, OR = 20.4). This study provides additional evidence. . .
CT Medical Descriptors:
***ulcerative colitis: ET, etiology**
DNA polymorphism
disease severity
marker gene
pathogenesis
disease predisposition
genetic risk
human
male
female
major clinical study
newborn
adolescent
aged
infant
preschool child
school child
adult
article
priority journal
*HLA DR1 antigen: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound

L15 ANSWER 25 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AB Angiotensin II (Ang II) plays an important role in post-myocardial infarction (MI) remodeling. Most Ang II effects related to remodeling involve activation of the type 1 receptor (AT1). Although the AT1 receptor is upregulated on cardiac fibroblasts post-MI, little is known about the mechanisms involved in the process. Consequently, we tested whether growth factors known to be present in the remodeling heart increased AT1 mRNA levels. Using quantitative competitive reverse transcription-polymerase chain reaction, we found that norepinephrine, endothelin, atrial natriuretic peptide, and bradykinin had no significant effect on AT1 mRNA

levels. Ang II, transforming growth factor-.beta.1, and basic fibroblast growth factor reduced AT1 mRNA levels (P<0.02). **Tumor necrosis factor**-.alpha. (**TNF**-.alpha.), however, produced a marked increase in AT1 mRNA. After 24 hours of **TNF**-.alpha. incubation, AT1 mRNA increased by 5-fold above control levels (P<0.01). The EC50 for the **TNF**-.alpha. effect was 4.6 ng/mL (0.2 nmol/L). Interleukin (IL)- 1.beta. caused a 2.4-fold increase, whereas IL-2 and IL-6 had no significant effect. Studies of **TNF**-.alpha. enhancement of AT1 mRNA levels demonstrate that the increase was not due to a change in transcript stability. **TNF**-.alpha. treatment for 48 hours also resulted in a 3-fold increase in AT1 surface receptor and a 2-fold increase in Ang II-induced production of inositol phosphates. The present findings provide evidence for **TNF**-.alpha. regulation of AT1 receptor density on cardiac fibroblasts. Because **TNF**-.alpha. concentration and AT1 receptor density increase in the myocardium after MI, these results raise the possibility that **TNF**-.alpha. modulates post-MI remodeling by enhancing Ang II effects on cardiac fibroblasts.

ACCESSION NUMBER: 1999280571 EMBASE
TITLE: **Tumor necrosis factor**-.alpha. upregulates angiotensin II type 1 receptors on cardiac fibroblasts.
AUTHOR: Gurantz D.; Cowling R.T.; Villarreal F.J.; Greenberg B.H.
CORPORATE SOURCE: Dr. B.H. Greenberg, Department of Medicine/Cardiology, UCSD Medical Center, 200 W Arbor Dr, San Diego, CA 92103-8411, United States. bgreenberg@ucsd.edu
SOURCE: Circulation Research, (6 Aug 1999) 85/3 (272-279). Refs: 41 ISSN: 0009-7330 CODEN: CIRUAL
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

TI **Tumor necrosis factor**-.alpha. upregulates angiotensin II type 1 receptors on cardiac fibroblasts.

AB . . . effect on AT1 mRNA levels. Ang II, transforming growth factor-.beta.1, and basic fibroblast growth factor reduced AT1 mRNA levels (P<0.02). **Tumor necrosis factor**-.alpha. (**TNF**-.alpha.), however, produced a marked increase in AT1 mRNA. After 24 hours of **TNF**-.alpha. incubation, AT1 mRNA increased by 5-fold above control levels (P<0.01). The EC50 for the **TNF**-.alpha. effect was 4.6 ng/mL (0.2 nmol/L). Interleukin (IL)- 1.beta. caused a 2.4-fold increase, whereas IL-2 and IL-6 had no significant effect. Studies of **TNF**-.alpha. enhancement of AT1 mRNA levels demonstrate that the increase was not due to a change in transcript stability. **TNF**-.alpha. treatment for 48 hours also resulted in a 3-fold increase in AT1 surface receptor and a 2-fold increase in Ang II-induced production of inositol phosphates. The present findings provide evidence for **TNF**-.alpha. regulation of AT1 receptor density on cardiac fibroblasts. Because **TNF**-.alpha. concentration and AT1 receptor density increase in the myocardium after MI, these results raise the possibility that **TNF**-.alpha. modulates post-MI remodeling by enhancing Ang II effects on cardiac fibroblasts.

CT Medical Descriptors:
*receptor upregulation
***heart infarction: ET, etiology**
fibroblast
heart ventricle remodeling
reverse transcription polymerase chain reaction
genetic transcription
receptor density
time
dose response
dissociation constant
heart
nonhuman
rat
animal cell
newborn
article
priority journal
***tumor necrosis factor alpha: PD, pharmacology**
*angiotensin receptor: EC, endogenous compound
noradrenalin: PD, pharmacology
endothelin: PD, pharmacology
atrial natriuretic factor: PD, pharmacology
bradykinin: PD, pharmacology
angiotensin: PD,. . .

L15 ANSWER 26 OF 50 CAPLUS COPYRIGHT 2002 ACS
AB **TNF**.alpha. contributes to **necrotizing enterocolitis** (NEC) pathogenesis. To date, this clin. entity of **neonates** has never been described in HIV-infected children. In 15 HIV-pos. children with histol. evidence of various intestinal lesions resembling NEC, the authors have studied serum **TNF**.alpha. and sol. **TNF** receptor concns. by ELISAs, and archived paraffin embedded intestinal tissues by in situ hybridization with DIG-labeled RNA probes for **TNF**.alpha. messenger transcripts. The authors found increased levels of **TNF**.alpha. and sol. receptors, proving **TNF**.alpha. system activation. They detected **TNF**.alpha. messenger transcripts in all cases, regardless of the presence of microbial pathogens at intestinal level. Since HIV can infect many cells of the gastrointestinal tract, also triggering the secretion of **TNF**.alpha., the authors concluded that factors contributing to NEC pathogenesis in HIV-infected children are complex. At least the nutritional and immunol. status are involved, other viral co-infections, opportunistic microbes (such as mycobacteria), and pathogenic activities of HIV. All together enhance both circulating **TNF**.alpha. system and its cytotoxic effects at intestinal level.
ACCESSION NUMBER: 2002:53380 CAPLUS
DOCUMENT NUMBER: 137:31926
TITLE: Evidence of **TNF** system activation and high expression of **TNF**.alpha. messenger transcripts in **necrotizing enterocolitis** of HIV-infected children
AUTHOR(S): Ispas, Doinita
CORPORATE SOURCE: "Dr. Victor Babes" Clinic Hospital for Infectious and Tropical Diseases, Bucharest, Rom.
SOURCE: Romanian Journal of Virology (1999), 50(1-4), 53-70
CODEN: RJVIFC; ISSN: 1018-0532
PUBLISHER: Editura Academiei Romane
DOCUMENT TYPE: Journal
LANGUAGE: English

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Evidence of **TNF** system activation and high expression of **TNF**.alpha. messenger transcripts in **necrotizing enterocolitis** of HIV-infected children

AB **TNF**.alpha. contributes to **necrotizing enterocolitis** (NEC) pathogenesis. To date, this clin. entity of **neonates** has never been described in HIV-infected children. In 15 HIV-pos. children with histol. evidence of various intestinal lesions resembling NEC, the authors have studied serum **TNF**.alpha. and sol. **TNF** receptor concns. by ELISAs, and archived paraffin embedded intestinal tissues by in situ hybridization with DIG-labeled RNA probes for **TNF**.alpha. messenger transcripts. The authors found increased levels of **TNF**.alpha. and sol. receptors, proving **TNF**.alpha. system activation. They detected **TNF**.alpha. messenger transcripts in all cases, regardless of the presence of microbial pathogens at intestinal level. Since HIV can infect many cells of the gastrointestinal tract, also triggering the secretion of **TNF**.alpha., the authors concluded that factors contributing to NEC pathogenesis in HIV-infected children are complex. At least the nutritional and immunol. status are involved, other viral co-infections, opportunistic microbes (such as mycobacteria), and pathogenic activities of HIV. All together enhance both circulating **TNF**.alpha. system and its cytotoxic effects at intestinal level.

ST **TNF** system activation **necrotizing enterocolitis** HIV infection children

IT Blood serum
(THF.alpha. and sol. **TNF** receptor of; **TNF** system activation in **necrotizing enterocolitis** of HIV-infected children)

IT Human
Human immunodeficiency virus 1
(**TNF** system activation in **necrotizing enterocolitis** of HIV-infected children)

IT Development, mammalian postnatal
(child; **TNF** system activation in **necrotizing enterocolitis** of HIV-infected children)

IT **Tumor necrosis factors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(of serum; **TNF** system activation in **necrotizing enterocolitis** of HIV-infected children)

IT Intestine, disease
(pseudomembranous enterocolitis; **TNF** system activation in **necrotizing enterocolitis** of HIV-infected children)

IT **Tumor necrosis factor** receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sol., of serum; **TNF** system activation in **necrotizing enterocolitis** of HIV-infected children)

L15 ANSWER 27 OF 50 USPATFULL

AB Inflammation can be treated or prevented altogether by administering a preparation comprising IgA. These preparations also can effect immunomodulation. Preferably, the preparation includes multimeric IgA and is essentially free of IgG in its various forms. Other compounds, such as antibiotics, antiphlogistic agents and antacids, also may be administered. Immunoglobulin A may also be used in vaccines to prevent inflammation. Additionally, an improved assay for evaluating anti-inflammatory activity is provided.

ACCESSION NUMBER: 1998:138436 USPATFULL
TITLE: Composition and method for preventing and treating inflammation with Immunoglobulin A
INVENTOR(S): Eibl, Martha, Vienna, Austria
Wolf, Hermann, Vienna, Austria
Mannhalter, Josef W., Vienna, Austria
Leibl, Heinz, Vienna, Austria
Linnau, Yendra, Vienna, Austria
PATENT ASSIGNEE(S): Immuno Aktiengesellschaft, Vienna, Austria (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5833984		19981110
APPLICATION INFO.:	US 1996-772264		19961223 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1994-198067, filed on 18 Feb 1994, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Eisenschenk, Frank C.
LEGAL REPRESENTATIVE: Foley & Lardner
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 7 Drawing Page(s)
LINE COUNT: 975
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . the immune system, especially the macrophage. Cells of the monocyte/macrophage lineage are the principal source of inflammatory cytokines such as **tumor necrosis factor** -alpha ("**TNF**-.alpha.") and interleukin 6 ("IL-6").

SUMM . . . inflammatory cytokines are produced in response to a variety of biological stimuli, such as lipopolysaccharide ("LPS") from gram negative bacteria. **TNF**-.alpha. and IL-6 play a central role in multiple effector functions and cellular interactions necessary to mount an effective host defense. . . and immune response. However, uncontrolled production of inflammatory cytokines is damaging to the host. For example, uncontrolled, LPS-induced release of **TNF** -.alpha. has been shown to be a central mediator of LPS-induced toxicity, including gram-negative endotoxic shock.

SUMM The injection of high doses of **TNF**-.alpha. into rats or mice induces the symptoms and lethality of septic shock. Furthermore, high serum levels of **TNF**-.alpha. correlate with the mortality of patients with meningococcemia or septic shock. High levels of **TNF**-.alpha. have also been found in **neonates** with **necrotizing enterocolitis**, suggesting that **TNF** -.alpha. may be involved in the pathogenesis of this disease. Indeed, endotoxin challenge and administration of **TNF**-.alpha. has induced bowel necrosis in an experimental model of neonatal **necrotizing enterocolitis**. Increased levels of IL-6 are found in a variety of clinical conditions including bacterial and viral meningitis and HIV infection.. . . inflammation, often with lethal results. The lethality of gram-negative bacteremia or endotoxemia has been prevented by the administration of specific, anti-**TNF** antibodies.

SUMM . . . preparations containing 73% IgA and 26% IgG, in terms of total immunoglobulin content, are capable of reducing the incidence of **necrotizing enterocolitis** when prophylactically

administered to low birth-weight infants. See Eibl et al., J. Clin. Imm. 10(6): 72S-79S (1990). This effect is. . .

SUMM . . . substance and evaluating the incubated cells for production of cytokines. Preferably, the cells are monocytes and the evaluated cytokines comprise **TNF**-.alpha., **TNF**-.beta., IL-1 or IL-6. Preferably, the results are compared to the cytokine production of a control, such as monocytes exposed to. . .

DRWD FIG. 1 depicts in graphical form that human serum IgA down-regulates **TNF**-.alpha. and IL-6 release in human monocytes activated with Haemophilus influenza type B.

DRWD FIG. 2 depicts in graphical form that human serum IgA down-regulates Hib-induced **TNF**-.alpha. and IL-6 release in human monocytes, while GM-CSF production following Hib-stimulation remains unchanged.

DRWD FIG. 3 depicts in graphical form the effect of human serum IgA on **TNF**-.alpha. and IL-6 release in monocytes stimulated with purified LPS.

DRWD FIG. 5 depicts in graphical form that human serum IgA down regulates **TNF**-.alpha. and IL-6 release in human monocytes, while human serum IgG has no effect.

DETD . . . inflammatory stimulus, which typically would cause the monocytes to express inflammatory cytokines. The amount of the expressed cytokines, such as **TNF**-.alpha., **TNF**-B, IL-1 and IL-6 is then determined. By comparing the amount expressed cytokines in the monocytes incubated with the test substance. . .

DETD . . . that IgA and IgG preparations contain comparable titers of antibodies that bind Hib, but only IgA decreases the levels of **TNF**-.alpha. and IL-6 production. The IgG preparations examined at similar concentrations in parallel experiments have no down-regulating effect on Hib-induced cytokine. . .

DETD . . . is largely monomeric, inhibits monocyte cytokine release. Heat aggregation, which forms IgA multimers, enhances the inhibitory effect of IgA on **TNF**-.alpha. release. A pharmaceutical preparation according to the present invention preferably contains multimeric IgA, which can be obtained by heating a. . .

DETD . . . the supernatants were distributed into aliquots which were kept frozen at -20.degree. C. for a maximum of three days until **TNF**-.alpha. and IL-6 concentrations were measured.

DETD **TNF**-.alpha., IL-6 and GM-CSF concentrations were determined in monocyte supernatants diluted 1:30 for **TNF**-.alpha., 1:5 for IL-6 or 1:2 for GM-CSF using commercially available ELISA kits (**TNF**-.alpha.-EASIA and IL-6-EASIA, Medgenix Diagnostics, Fleurus, Belgium and Quantikine Human GM-CSF Immunoassay, R&D Systems, Minneapolis, Minn.). The monoclonal antibodies specific for the respective cytokine used in **TNF**-.alpha. and IL-6 assays are non-neutralizing antibodies that react with an epitope on the cytokine molecule different than the receptor binding. . . should not be biased by the presence of soluble cytokine receptors or inhibitors. Results are expressed as pg/ml of IL-6, **TNF**-.alpha. or GM-CSF as calculated from a standard curve derived by linear regression of the log-transformed concentrations of the cytokine standards. . .

DETD Effect of IgA on **TNF**-.alpha. and IL-6 release in human monocytes

DETD . . . inflammatory cytokines when triggered by gram negative bacteria such as Hib. The effect of IgA on the Hib-induced release of **TNF**-.alpha. and IL-6 was examined.

DETD . . . at the indicated concentrations. Control wells contained monocytes cultured in the presence of Hib alone. After the 24-hour incubation period, **TNF**-.alpha. and IL-6 concentrations in cell-free supernatants were determined by ELISA. Results are expressed as pg/ml (mean.+-.SEM of 8 individual experiments). Monocytes cultured in medium alone released 18.+-.9 pg/ml of **TNF**-.alpha. and 61.+-.50 pg/ml of IL-6. Background cytokine release in cultures containing IgA only was 31.+-.20 pg/ml (0.1 mg/ml) and 562.+-.263 pg/ml (10 mg/ml) for **TNF**-.alpha., and 255.+-.148 and 121.+-.82 pg/ml for IL-6.

DETD . . . of Hib (1.times.10.sup.6 bacteria/ml) under serum-free conditions (in RPMI suppl. containing 1% HSA) induced the release of significant levels of **TNF**-.alpha. (43198.+-.6912 pg/ml) and IL-6 (10990.+-.669 pg/ml). The asterisk ("*") denotes a statistically significant difference between IgA-treated and control cells (p<0.005,. . .

DETD . . . monocytes and Hib resulted in a dose-dependent decrease in the release of both cytokines (FIG. 1). The IgA-mediated inhibition of **TNF**-.alpha. release was maximal at 3 mg/ml (% inhibition, mean.+-.SEM of 8 experiments: **TNF**-.alpha. 65.+-.5, significant difference as compared to cultures with Hib alone was p=0.001636 with the Mann-Whitney U test, and was not. . .

DETD TABLE 1

Monocyte treatment	Cytokine release (pg/ml) **TNF**-.alpha.	IL-6	cells per well (10.sup.5)	monocyte purity (%)
Medium	33 .+-. 20	6 .+-. 6	0.8 .+-. 0.1.sup.(1)	71 .+-. 8.9.sup.(2)
IgA.sup.(3)	127 .+-. 55			

. . .

DETD FIG. 2 shows that human serum IgA down-regulates Hib-induced **TNF**-.alpha. and IL-6 release in human monocytes, but has no effect on GM-CSF production following Hib-stimulation in this model. First, adherent. . . with Hib in the presence or absence of IgA (10 mg/ml) as was explained for the experiment of FIG. 1. **TNF**-.alpha., IL-6 and GM-CSF concentrations were determined by ELISA, and results are given as pg/ml (mean.+-.SEM of 8 individual experiments). Background cytokine releases of **TNF**-.alpha. and IL-6 are described in the discussion for FIG. 1. Monocytes cultured in medium alone released no detectable levels of. . .

DETD Even high concentrations of IgA (10 mg/ml) had no inhibitory effect on GM-CSF release following Hib-stimulation, while **TNF**-.alpha. and IL-6 release measured in the same supernatants were significantly decreased. Thus, down-modulation of **TNF**-.alpha. and IL-6 release was not due to a generally decreased ability of the monocytes to release cytokines following stimulation with. . .

DETD The decrease in **TNF**-.alpha. and IL-6 concentration measured in the monocyte supernatants in the presence of IgA was due to a true down-modulation of. . . mg/ml of human serum IgA or IgG to supernatant of Hib-activated monocytes had no significant effect on the

amount of **TNF**-.alpha. or IL-6 detected, which rules out a possible interference of IgA or IgG antibodies with the measurement of these cytokines. . .

DETD TABLE 2

		cytokine release.sup.(1) (pg/ml).sup.(2) **TNF**-.alpha. IL-6
No antibody		
	No antibody	9412 .+-. 3108
		3054 .+-. 1456
IgA	10	9218 .+-. 3674
		2744 .+-. 1622
IgA	25	9187 .+-.. . .

DETD Furthermore, the observed IgA-mediated decrease in **TNF**-.alpha. and IL-6 release was not an artifact due to high protein concentrations in cultures containing IgA. Addition of equivalent amounts. . . concentration of 20 mg/ml of HSA had no effect on Hib-induced release of these cytokines. The results were as follows: **TNF**-.alpha. release, pg/ml [% of control]: (i) HSA 10 mg/ml 18540.+-.5678, HSA 20 mg/ml 14922.+-.5040 [84.+-.8%] and (ii) IL-6 release, pg/mil:. . .

DETD The IgA-mediated inhibition of Hib-induced **TNF**-.alpha. and IL-6 release was not enhanced by facilitating the interaction of IgA with Hib. The data demonstrated that preincubation of. . . effect (percent inhibition of cytokine release, mean.+-.SEM: (1) IgA (10 mg/ml) and Hib added to the cells without preincubation (n=8): **TNF** -.alpha. 63.+-.7, IL-6 73.+-.11 and (2) Hib preincubated with IgA for 30 minutes at 37.degree. C. before addition of Hib and IgA to the cells (n=11): **TNF**-.alpha. 59.+-.9, IL-6 51.+-.18).

DETD The experiments depicted in FIG. 3 show that IgA also down-regulates **TNF**-.alpha. and IL-6 release in response to stimulation with a soluble stimulus, LPS purified from E. coli. First, adherent monocytes were. . . Control wells contained monocytes and LPS, monocytes and IgA, or monocytes cultured in RPMI-HSA alone. After the 24-hour incubation period, **TNF**-.alpha. and IL-6 release was determined in the cell-free supernatants by ELISA. The results presented in FIG. 3 are expressed as. . . absence of IgA), calculated as described previously (mean.+-.SEM of six experiments). Control cells stimulated with LPS released 16657.+-.5536 pg/ml of **TNF**-.alpha. and 1110.+-.294 pg/ml of IL-6. Wilcoxon matched-pairs signed-ranks test of the difference in cytokine levels (pg/ml) between IgA-treated and control. . .

DETD The results in FIG. 3 shows that the dose response of the IgA-mediated inhibition was comparable for **TNF**-.alpha. and IL-6 release.

DETD Effect of multimeric IgA on Hib-induced **TNF**-.alpha. and IL-6 release

DETD The data in FIG. 4 show that the immunomodulating effect of human serum IgA on **TNF**-.alpha. release is significantly enhanced if IgA is present in a multimeric form.

DETD . . . 10 mg/ml). Control cultures were set up with monocytes and Hib alone. After 24 hours, cell-free supernatants were collected and **TNF**-.alpha. and IL-6 concentrations were determined by ELISA. Results are expressed as pg/ml (mean.+-.SEM of 6 individual experiments).

DETD In six experiments, monomeric IgA reduced **TNF**-.alpha. release

by 48.+-.9%, while the inhibition of **TNF**-.alpha. release induced by multimeric IgA (heat-aggregated) in parallel was 73.+-.5% (mean.+-.SEM, n=6, p=0.018686 as compared to % inhibition by monomeric. . .

DETD FIG. 5 shows that IgA significantly reduced the release of **TNF** -.alpha. and IL-6 by adherent monocytes following stimulation with Hib, but IgG examined at a similar concentration had no effect on. . . monocytes adhered/well/ml) in the presence of Hib (1.times.10.sup.6 bacteria/ml/well) and IgA or IgG (final concentration 10 mg/ml) for 24 hours. **TNF**-.alpha. and IL-6 levels were then determined in cell-free supernatants by ELISA. Results represent pg/ml (mean.+-.SEM of 8 individual experiments).

DETD . . . served as a positive control, and cells cultured in medium alone without Hib were examined to determine background cytokine release (**TNF**-.alpha. 202.+-.123 pg/ml, IL-6 15.+-.8 pg/ml). Monocytes cultured in the presence of IgG (10 mg/ml) alone released 449.+-.182 pg/ml of **TNF**-.alpha. and 9.+-.5 pg/ml of IL-6; the supernatants of cells treated with IgA (10 mg/ml) alone contained 721.+-.244 pg/ml of **TNF**-.alpha. and 6.+-.2 pg/ml of IL-6. Statistical evaluation of the difference between cytokine release in the presence of IgA or IgG. . .

DETD There are several possible explanations for the inhibitory effect of IgA on Hib-induced **TNF**-.alpha. and IL-6 release. For instance, IgA could interfere with the Hib-induced stimulation of cytokine release by blocking the binding of. . . to the monocyte surface membrane. This would subsequently lead to decreased levels of cytokine release. The IgA-mediated decrease in Hib-induced **TNF**-.alpha. and IL-6 release could also be the result of a true down-regulation of cytokine production and/or cytokine release in Hib-stimulated. . .

DETD . . . the following 21-hour incubation period (Hib.fwdarw.IgA). Cell-free supernatants were collected after the 21-hour incubation following the 3-hour Hib stimulation, and **TNF**-.alpha. and IL-6 concentrations were determined by ELISA. Control cells that were stimulated for 3 hours with Hib, washed, and then cultured for 21 hours in RPMI-HSA without IgA (Hib.fwdarw.Med) released 4939.+-.1588 pg/ml of **TNF**-.alpha. and 1626.+-.728 pg/ml of IL-6. Cytokine release in the IgA-treated cells is expressed as percentage of this control cytokine release,. . . appropriate media changes and were exposed to IgA or medium alone contained between 65.+-.54 (Med..fwdarw.IgA) and 113.+-.38 (IgA.fwdarw.IgA) pg/ml of **TNF**-.alpha. and between 8.+-.8 (IgA Med.) and 21.+-.14 (Med..fwdarw.IgA) pg/ml of IL-6.

DETD Supernatants collected immediately after the 3-hour stimulation with Hib contained only very low amounts of **TNF**-.alpha. (502.+-.178 pg/ml) and IL-6 (288.+-.124 pg/ml, mean.+-.SEM of three experiments), while supernatants collected after a 21-hour incubation following the 3-hour stimulation with Hib (after the stimulus had been removed by extensive washing) contained 3385.+-.463 pg/ml of **TNF**-.alpha. and 1900.+-.953 pg/ml of IL-6, indicating that 88.+-.3% of the total **TNF**-.alpha. and 86.+-.3% of the total IL-6 that is induced by 3-hour stimulation with Hib is released during the 21 hours following stimulation. Continuous stimulation for 24 hours with Hib resulted in 2 to 3 fold higher levels of **TNF**-.alpha. (12849.+-.2904 pg/ml) and IL-6 (4278.+-.766 pg/ml) as compared to the levels of these cytokines in the 21-hour cultures of 3-hour. . .

DETD As shown in FIG. 7, monocytes stimulated for 3 hours with Hib released

markedly reduced levels of **TNF**-.alpha. and IL-6 when IgA (10 mg/ml) was added to the system during the time of cytokine release, after the Hib. . . by extensive washing (Hib.fwdarw.IgA). In addition, IgA added to the cell cultures during the 3-hour stimulation with Hib also decreased **TNF**-.alpha. and IL-6 release during the 21 hours following stimulation, after IgA and stimulus had been removed by extensive washing (Hib+IgA-Med.).

DETD . . . (the first three hours) and cytokine release in the absence of stimulus (the following 21 hours), the inhibitory effect on **TNF**-.alpha. and IL-6 release was maximal (Hib+IgA.fwdarw.IgA).

DETD In sum, IgA down-regulates the release of **TNF**-.alpha. and IL-6 in activated human monocytes with the particulate stimulus Hib. **TNF**-.alpha. and IL-6 release are down-regulated when IgA is present during the time of continuous stimulation of monocytes with Hib.

IgA also inhibits the release of **TNF**-.alpha. and IL-6, if present during cytokine induction. Additionally, IgA is inhibitory if added to Hib-pretreated monocytes after the induction of. . . removed by extensive washing. When IgA is present both during cytokine induction and cytokine release, the IgA mediated down-regulation of **TNF**-.alpha. and IL-6 production is maximal. This strongly indicates not only a preventive effect of IgA on inflammatory reactions but also. . .

L15 ANSWER 28 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB In addition to its role as a survival factor, nerve growth factor (NGF) has been implicated in initiating apoptosis in restricted cell types both during development and after terminal cell differentiation. NGF binds to the TrkA tyrosine kinase and the p75 neurotrophin receptor, a member of the **tumor necrosis factor** cytokine family.
To understand the mechanisms underlying survival versus death decisions, the TrkA receptor was introduced into oligodendrocyte cell cultures that undergo apoptosis in a p75-dependent manner. Here we report that activation of the TrkA NGF receptor in oligodendrocytes negates cell death by the p75 receptor. TrkA-mediated rescue from apoptosis correlated with mitogen-activated protein kinase activation. Concurrently, activation of TrkA in oligodendrocytes resulted in suppression of c-jun kinase activity initiated by p75, whereas induction of NF.kappa.B activity by p75 was unaffected. These results indicate that TrkA-mediated rescue involves not only activation of survival signals but also simultaneous suppression of a death signal by p75. The selective interplay between tyrosine kinase and cytokine receptors provides a novel mechanism that achieves alternative cellular responses by merging signals from different ligand-receptor systems.

ACCESSION NUMBER: 1998136217 EMBASE
TITLE: Competitive signaling between TrkA and p75 nerve growth factor receptors determines cell survival.
AUTHOR: Sung Ok Yoon; Casaccia-Bonnefil P.; Carter B.; Chao M.V.
CORPORATE SOURCE: M.V. Chao, New York University Medical Center, 540 First Avenue, New York, NY 10016, United States
SOURCE: Journal of Neuroscience, (1 May 1998) 18/9 (3273-3281). Refs: 71
ISSN: 0270-6474 CODEN: JNRSDS
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy

029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB . . . after terminal cell differentiation. NGF binds to the TrkA tyrosine kinase and the p75 neurotrophin receptor, a member of the **tumor necrosis factor** cytokine family. To understand the mechanisms underlying survival versus death decisions, the TrkA receptor was introduced into oligodendrocyte cell cultures. . .
CT Medical Descriptors:
***nerve cell necrosis**
*cell survival
apoptosis
cell differentiation
oligodendroglia
enzyme activity
nonhuman
rat
controlled study
animal cell
newborn
article
priority journal
*nerve growth factor: EC, endogenous compound
*nerve growth factor receptor: EC, endogenous compound
*protein tyrosine kinase: EC, endogenous compound
*neurotrophin receptor: EC,. . .

L15 ANSWER 29 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AB We studied, using organotypic hippocampal slices in culture, the role of pro-inflammatory cytokines, oxygen radicals and nitric oxide in neuronal death induced either by endotoxic insult [interferon (IFN) .gamma., 24 h followed by lipopolysaccharide, 24 h] or by glutamate receptor-mediated excitotoxic insult. We demonstrated that neuronal death induced by endotoxic insult was absolutely dependent on the synthesis of tumour necrosis factor alpha (**TNF**-.alpha.). Indeed, **TNF** -.alpha. antibodies and SB203580, an inhibitor of p38 stress kinase known to block **TNF**-.alpha. and other cytokine synthesis, completely protected neurons from the endotoxic insult. Inhibiting oxygen radical and nitric oxide productions also reduced the endotoxic shock. We also showed that after priming the cultures with IFN-.gamma., **TNF**-.alpha. was unable to induce neuronal death unless oxygen-free radicals were exogenously provided. In contrast, although glutamate receptor-induced excitotoxicity was associated with a low **TNF**-.alpha. synthesis and a modest activation of p38 stress kinase, neither **TNF** -.alpha. antibodies nor SB203580 were able to decrease excitotoxic neuronal insult. We did not reduce glutamate receptor-induced neuronal death with superoxide dismutase plus catalase. In conclusion, although inflammation follows glutamate receptor-mediated neurotoxicity, the mechanisms by which an endotoxic insult triggers neuronal death are different from those involved in excitotoxicity.
ACCESSION NUMBER: 1999054508 EMBASE
TITLE: The neuronal death induced by endotoxic shock but not that induced by excitatory amino acids requires **TNF** -.alpha..
AUTHOR: De Bock F.; Denjard B.; Domand J.; Bockaert J.; Rondouin G.
CORPORATE SOURCE: F. De Bock, CNRS UPR 9023, Laboratoire Medecine Experimentale, Institut de Biologie, Bd Henri IV, 34060 Montpellier Cedex, France. debock@ccipe.montp.inserm.fr

SOURCE: European Journal of Neuroscience, (1998) 10/10 (3107-3114).
Refs: 28
ISSN: 0953-816X CODEN: EJONEI
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English

TI The neuronal death induced by endotoxic shock but not that induced by excitatory amino acids requires **TNF**-.alpha..

AB . . . We demonstrated that neuronal death induced by endotoxic insult was absolutely dependent on the synthesis of tumour necrosis factor alpha (**TNF**-.alpha.). Indeed, **TNF**-.alpha. antibodies and SB203580, an inhibitor of p38 stress kinase known to block **TNF** -.alpha. and other cytokine synthesis, completely protected neurons from the endotoxic insult. Inhibiting oxygen radical and nitric oxide productions also reduced the endotoxic shock. We also showed that after priming the cultures with IFN-.gamma., **TNF**-.alpha. was unable to induce neuronal death unless oxygen-free radicals were exogenously provided. In contrast, although glutamate receptor-induced excitotoxicity was associated with a low **TNF**-.alpha. synthesis and a modest activation of p38 stress kinase, neither **TNF**-.alpha. antibodies nor SB203580 were able to decrease excitotoxic neuronal insult. We did not reduce glutamate receptor-induced neuronal death with superoxide. . .

CT Medical Descriptors:
***nerve cell necrosis**
*septic shock
hippocampus
cytokine production
neuroprotection
enzyme activation
inflammation
neurotoxicity
nonhuman
rat
controlled study
animal tissue
newborn
article
priority journal
*excitatory amino acid
***tumor necrosis factor alpha: EC, endogenous compound**
oxygen radical: EC, endogenous compound
nitric oxide: EC, endogenous compound
cytokine: EC, endogenous compound
gamma interferon
lipopolysaccharide
glutamate receptor: EC, endogenous compound
tumor necrosis factor alpha antibody
4 (4 fluorophenyl) 2 (4 methylsulfinylphenyl) 5 (4 pyridyl)imidazole
heat shock protein: EC, endogenous compound
protein kinase: EC, endogenous. . .

L15 ANSWER 30 OF 50 CAPLUS COPYRIGHT 2002 ACS

AB Platelet activating factor (PAF) has been reported to play a role in the development of **necrotizing enterocolitis** of the

newborn. In an adult rat **necrotizing enterocolitis** model, pretreatment with recombinant human PAF acetylhydrolase (r-PAF-AH) completely protected the animals against **necrotizing enterocolitis** development. The protection was dose- and time-dependent. The plasma PAF-AH activity required for **necrotizing enterocolitis** prevention was similar to that previously obsd. following dexamethasone administration. The administration of a non-hydrolyzable analog of PAF, cPAF, generated **necrotizing enterocolitis** which was not altered by the administration of r-PAF-AH. The administration of low doses of lipopolysaccharide (LPS) in combination with **tumor necrosis factor**-.alpha. or high doses of LPS alone caused a severe hemorrhage of the lamina propria of the intestine. The hemorrhagic lesions were similar to those obsd. with **necrotizing enterocolitis**. In both cases necrosis was not obsd. The administration of r-PAF-AH prevented the hemorrhagic infiltration and the intestine appeared to be normal as judged by both gross and microscopic examn. When PAF and LPS were injected i.p., **necrotizing enterocolitis** developed in approx. 80% of the animals. Again, pretreatment with r-PAF-AH completely protected against **necrotizing enterocolitis** development. These findings provide further evidence for the central role of PAF in the development of **necrotizing enterocolitis** and a possible mechanism for the treatment of **necrotizing enterocolitis** is suggested.

ACCESSION NUMBER: 1999:128424 CAPLUS
DOCUMENT NUMBER: 130:350642
TITLE: Role of platelet activating factor in **necrotizing enterocolitis** development in the rat
AUTHOR(S): Muguruma, K.; Furukawa, M.; Tjoelker, L. W.; Lee, E. L.; Dietsch, G.; Gray, P. W.; Zhao, B.; Johnston, J. M.
CORPORATE SOURCE: Departments of Biochemistry, University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA
SOURCE: Prenatal and Neonatal Medicine (1998), 3(6), 571-579
CODEN: PNMEFT; ISSN: 1359-8635
PUBLISHER: Parthenon Publishing Group Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Role of platelet activating factor in **necrotizing enterocolitis** development in the rat

AB Platelet activating factor (PAF) has been reported to play a role in the development of **necrotizing enterocolitis** of the **newborn**. In an adult rat **necrotizing enterocolitis** model, pretreatment with recombinant human PAF acetylhydrolase (r-PAF-AH) completely protected the animals against **necrotizing enterocolitis** development. The protection was dose- and time-dependent. The plasma PAF-AH activity required for **necrotizing enterocolitis** prevention was similar to that previously obsd. following dexamethasone administration. The administration of a non-hydrolyzable analog of PAF, cPAF, generated **necrotizing enterocolitis** which was not altered by the administration of r-PAF-AH. The administration of low doses of

lipopolysaccharide (LPS) in combination with **tumor necrosis factor**-.alpha. or high doses of LPS alone caused a severe hemorrhage of the lamina propria of the intestine. The hemorrhagic lesions were similar to those obsd. with **necrotizing enterocolitis**. In both cases necrosis was not obsd. The administration of r-PAF-AH prevented the hemorrhagic infiltration and the intestine appeared to be normal as judged by both gross and microscopic examn. When PAF and LPS were injected i.p., **necrotizing enterocolitis** developed in approx. 80% of the animals. Again, pretreatment with r-PAF-AH completely protected against **necrotizing enterocolitis** development. These findings provide further evidence for the central role of PAF in the development of **necrotizing enterocolitis** and a possible mechanism for the treatment of **necrotizing enterocolitis** is suggested.

ST platelet activating factor **necrotizing enterocolitis**

IT Lipopolysaccharides
Tumor necrosis factors
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(platelet activating factor in **necrotizing enterocolitis** development)

IT Intestine, disease
(pseudomembranous enterocolitis; platelet activating factor in **necrotizing enterocolitis** development)

IT 65154-06-5, Platelet activating factor
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(platelet activating factor in **necrotizing enterocolitis** development)

IT 76901-00-3, PAF acetylhydrolase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(recombinant plasma; platelet activating factor in **necrotizing enterocolitis** development)

L15 ANSWER 31 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB Necrotizing entercolitis (NEC) is an important neonatal disease with a high mortality rate. Inflammatory mediators, such as mainly platelet-activating factor (PAF), leukotrienes (LT) and **tumor necrosis factor** play an important role in the genesis of NEC. Diets in .OMEGA..dblarw.3 (n-3) fatty acids appear to have an antiinflammatory effect, which is thought to be due to decreased active prostaglandins and leukotrienes production after incorporation of these fatty acids into cell membranephospholipids. We investigated the protective effect of fish oil (source of n-3 fatty acids) on hypoxia-induced model of NEC. Young mice were divided into three groups group 1 mice were fed standard chow (n-3 fatty acids-free), group 2 was fed a chow supplemented by 10% fish oil for 4 weeks. Group 3 mice served as control. We examined the intestinal lesions by light microscopy and measured intestinal tissue PAF and LB4 levels in hypoxia-induced model of NEC. Significantly increased intestinal PAF and LTB4 levels were found in group 1 mice when compared to group 2 and group 3 mice. The histopathology

of the intestinal lesions in group 1 animals was characteristic of ischemic injury. In the n-3 fatty acids-supplemented animals these lesions were milder. The present study shows that endogenously released PAF and LTB4 play an important role in mediating hypoxia-induced intestinal necrosis. The present study also suggests that dietary supplementation with n-3 fatty acids suppress intestinal PAF and LTB4 generation in hypoxia-induced bowel necrosis. The intestinal protective effect of n-3 fatty acids in an experimental model of NEC may open new insight into the treatment and preventation of NEC in **neonates**.

ACCESSION NUMBER: 1998198600 EMBASE

TITLE: Effect of dietary n-3 fatty acids on hypoxia-induced **necrotizing enterocolitis** in young mice. n-3 fatty acids alter platelet-activating factor and leukotriene B4 production in the intestine.

AUTHOR: Akisu M.; Baka M.; Coker I.; Kultursay N.; Huseyinov A.

CORPORATE SOURCE: Dr. M. Akisu, Department of Pediatrics, Ege University Medical Faculty, TR-35100 Bornova, Izmir, Turkey. makisu@hotmail.com

SOURCE: Biology of the Neonate, (1998) 74/1 (31-38). Refs: 36 ISSN: 0006-3126 CODEN: BNEOBV

COUNTRY: Switzerland

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

TI Effect of dietary n-3 fatty acids on hypoxia-induced **necrotizing enterocolitis** in young mice. n-3 fatty acids alter platelet-activating factor and leukotriene B4 production in the intestine.

AB . . . an important neonatal disease with a high mortality rate. Inflammatory mediators, such as mainly platelet-activating factor (PAF), leukotrienes (LT) and **tumor necrosis factor** play an important role in the genesis of NEC. Diets in .OMEGA..dblarw.3 (n-3) fatty acids appear to have an antiinflammatory. . . fatty acids in an experimental model of NEC may open new insight into the treatment and preventation of NEC in **neonates**.

CT Medical Descriptors:
*fat intake
***necrotizing enterocolitis**
*hypoxia
intestine injury
microscopy
histopathology
intestine ischemia
nonhuman
mouse
animal experiment
animal model
controlled study
article
priority journal
*omega 3 fatty acid
fish oil
thrombocyte activating factor: EC, endogenous compound
leukotriene b4: EC, endogenous. . .

L15 ANSWER 32 OF 50 EMBASE

AB To evaluate the role of **tumor necrosis factor** -.alpha. (**TNF**-.alpha.) in neuronal injury in experimental group B streptococcal meningitis, infected neonatal rats were treated with a monoclonal antibody against **TNF**-.alpha. (20 mg/kg intraperitoneally) or saline given at the time of infection. Histopathology after 24 h showed necrosis in the cortex and apoptosis in the hippocampal dentate gyrus. Treated animals had significantly less hippocampal injury than did controls (P < .001) but had similar cortical injury and cerebrospinal fluid (CSF) inflammation. The antibody was then administered directly intracisternally (170 .mu.g) to test whether higher CSF concentrations reduced inflammation or cortical injury. Again, hippocampal apoptosis was significantly reduced (P < .01), while cortical injury and inflammation were not. Thus, **TNF**-.alpha. played a critical role in neuronal apoptosis in the hippocampus, while it was not essential for the development of inflammation and cortical injury in this model.

ACCESSION NUMBER: 97259962 EMBASE
DOCUMENT NUMBER: 1997259962
TITLE: **Tumor necrosis factor**-.alpha. contributes to apoptosis in hippocampal neurons during experimental group B streptococcal meningitis.
AUTHOR: Bogdan I.; Leib S.L.; Bergeron M.; Chow L.; Tauber M.G.
CORPORATE SOURCE: Dr. M.G. Tauber, Institute for Medical Microbiology, University of Berne, Friedbuhlstrasse 51, 3010 Berne, Switzerland
SOURCE: Journal of Infectious Diseases, (1997) 176/3 (693-697). Refs: 28
ISSN: 0022-1899 CODEN: JIDIAQ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

TI **Tumor necrosis factor**-.alpha. contributes to apoptosis in hippocampal neurons during experimental group B streptococcal meningitis.

AB To evaluate the role of **tumor necrosis factor** -.alpha. (**TNF**-.alpha.) in neuronal injury in experimental group B streptococcal meningitis, infected neonatal rats were treated with a monoclonal antibody against **TNF**-.alpha. (20 mg/kg intraperitoneally) or saline given at the time of infection. Histopathology after 24 h showed necrosis in the cortex. . . or cortical injury. Again, hippocampal apoptosis was significantly reduced (P < .01), while cortical injury and inflammation were not. Thus, **TNF** -.alpha. played a critical role in neuronal apoptosis in the hippocampus, while it was not essential for the development of inflammation. . .

CT Medical Descriptors:
*apoptosis
*bacterial meningitis: DT, drug therapy
*bacterial meningitis: ET, etiology
*hippocampus
***nerve cell necrosis: ET, etiology**
***nerve cell necrosis: DT, drug therapy**
*streptococcus agalactiae
animal experiment

animal model
animal tissue
article
brain injury: DT, drug therapy
brain injury: ET, etiology
cerebrospinal fluid analysis
controlled study
dentate gyrus
encephalitis: ET, etiology
encephalitis: DT, drug therapy
granule cell
intracisternal drug administration
intraperitoneal drug administration
newborn
nonhuman
priority journal
rat
subcutaneous drug administration
drug therapy
etiology
*monoclonal antibody
***tumor necrosis factor alpha**
***tumor necrosis factor alpha antibody**
ceftriaxone: DT, drug therapy
sodium chloride

L15 ANSWER 33 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB Coagulation necrosis, inflammation, and hemorrhage are pathologic hallmarks of **necrotizing enterocolitis** (NEC). Because cytokines are peptides that mediate inflammatory cell recruitment and amplify the immune response, several of the inflammatory cytokines have been implicated in NEC. We hypothesized that mRNA levels for the interrelated cytokines interleukin- 1.beta. (IL-1.beta.), **tumor necrosis factor**-.alpha. (**TNF**-.alpha.), IL-6, and the neutrophil chemotactic factor IL-8 would be increased in NEC and would be associated with the presence of inflammation. In this study, we determined the relative levels and localization of mRNA for these cytokines in surgical pathology archival intestinal tissue from 29 premature infants with acute NEC and 15 control infants with congenital intestinal malformations using a novel quantitative in situ hybridization technique. Compared with controls, there were higher IL-1.beta. mRNA levels in full-thickness sections and higher **TNF**-.alpha. mRNA levels in full-thickness and mucosa sections of acute NEC samples, suggesting a potential role far these cytokines in the pathogenesis of local inflammation in NEC. IL-6 and IL-8 mRNA levels were similar in samples of control and acute NEC cases. Analysis of covariance including all subjects showed that the presence of acute inflammation was associated with increased IL-1.beta. mRNA levels in mucosa (P =.035) and increased IL-8 in full-thickness sections (P =.005) and mucosa (P =.01). In four of five NEC cases in which intestinal specimens were available from reanastomosis surgery, cytokine mRNA levels decreased to low or undetectable levels. These data suggest that the inflammatory cytokines are involved in neutrophil recruitment and augmentation of the inflammatory response in neonatal intestine.

ACCESSION NUMBER: 97188102 EMBASE
DOCUMENT NUMBER: 1997188102
TITLE: Inflammatory cytokine mRNAs in surgical specimens of **necrotizing enterocolitis** and normal **newborn** intestine.

AUTHOR: Viscardi R.M.; Lyon N.H.; Sun C.-C.J.; Hebel J.R.; Hasday J.D.

CORPORATE SOURCE: Dr. R.M. Viscardi, Department of Pediatrics, University of Maryland Hospital, Room N5W68, 22 South Greene Street, Baltimore, MD 21201, United States

SOURCE: Pediatric Pathology and Laboratory Medicine, (1997) 17/4 (547-559).
Refs: 42
ISSN: 1077-1042 CODEN: PPLMER

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation

LANGUAGE: English

SUMMARY LANGUAGE: English

TI Inflammatory cytokine mRNAs in surgical specimens of **necrotizing enterocolitis** and normal **newborn** intestine.

AB Coagulation necrosis, inflammation, and hemorrhage are pathologic hallmarks of **necrotizing enterocolitis** (NEC). Because cytokines are peptides that mediate inflammatory cell recruitment and amplify the immune response, several of the inflammatory cytokines have been implicated in NEC. We hypothesized that mRNA levels for the interrelated cytokines interleukin-1.beta. (IL-1.beta.), **tumor necrosis factor**-.alpha. (**TNF**-.alpha.), IL-6, and the neutrophil chemotactic factor IL-8 would be increased in NEC and would be associated with the presence of. . . novel quantitative in situ hybridization technique. Compared with controls, there were higher IL-1.beta. mRNA levels in full-thickness sections and higher **TNF** -.alpha. mRNA levels in full-thickness and mucosa sections of acute NEC samples, suggesting a potential role far these cytokines in the. . .

CT Medical Descriptors:
*inflammation
***necrotizing enterocolitis**
anastomosis
article
bleeding
blood clotting disorder
clinical article
controlled study
human
human tissue
immune response
in situ hybridization
intestine malformation
neutrophil chemotaxis
newborn
onset age
prematurity
priority journal
protein localization
*cytokine
*interleukin 1beta
*interleukin 6
*interleukin 8
***tumor necrosis factor alpha**
messenger rna

L15 ANSWER 34 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB Purpose: The role of inflammatory cytokines in the pathogenesis of **necrotizing enterocolitis** (NEC) is still undefined.

Elevated levels of interleukin (IL)-6 and **tumor necrosis factor** (**TNF**)-.alpha. have been measured in infants with NEC, while elevated levels of nitric oxide (NO) have been reported in **newborn** infants with clinical sepals. However, the cellular source of the NO or cytokines is unknown. The authors hypothesized that local intestinal production of NO induced by cytokines may contribute to the pathogenesis of bowel necrosis in NEC by inducing apoptosis (programmed cell death) or necrosis of the enterocytes. We examined the levels of inflammatory cytokines and NO in the intestine of infants undergoing surgical resection for NEC, and the cellular localization of human inducible NO synthase (NOS- 2) in the inflamed gut. Methods: We compared 15 patients undergoing bowel resection for NEC, with six infants (of similar age) undergoing intestinal resection for ileal atresia or stricture, meconium peritonitis, intussusception, or cecal perforation (control). Diagnosis of NEC was confirmed histologically. Representative segments of the surgical specimen were examined for messenger RNA (mRNA) for NOS-2 by Northern blotting and in situ hybridization. Cytokine mRNA was measured by polymerase chain reaction (PCR) because mRNA could not be detected by Northern blotting. The site of NO production was determined by in situ hybridization and immunohistochemistry. Apoptosis was measured using in situ DNA strand break extension (TUNEL). Nitrotyrosine immunoreactivity was assessed to determine if NO mediates cellular injury via peroxynitrite formation. Results: Messenger RNA for NOS- 2 was detected in nearly all patients with NEC except for one infant who underwent proximal diverting jejunostomy alone, and who did not have histological evidence of NEC at that site. NOS-2 mRNA was detected less frequently in control patients. In situ hybridization and immunohistochemistry showed that the enterocytes were the predominant source of NOS-2 activity in the intestine of NEC patients. Extensive apoptosis was seen in enterocytes in the apical villi of infants with NEC, and correlated with nitrotyrosine staining. NOS-2 activity was markedly diminished at the time of stoma closure, but remained elevated in infants who died from progressive disease, PCR showed variable cytokine mRNA expression in the intestine. Transforming growth factor (TGF)-.beta. expression was nearly identical in NEC and control. However, interferon (IFN)-.gamma. was present in 9 of 10 NEC, but only in one of six control patients. Conclusion: The data show that NO is produced in large quantity by enterocytes in the intestinal wall of infants with NEC and leads to apoptosis of enterocytes in apical villi through peroxynitrite formation.

ACCESSION NUMBER: 97057266 EMBASE
DOCUMENT NUMBER: 1997057266
TITLE: The role of inflammatory cytokines and nitric oxide in the pathogenesis of **necrotizing enterocolitis**
.
AUTHOR: Ford H.R.; Watkins S.; Reblock K.; Rowe M.; Lally K.P.
CORPORATE SOURCE: Dr. H.R. Ford, Children's Hospital of Pittsburgh, 3705 Fifth Ave, Pittsburgh, PA 15213-2583, United States
SOURCE: Journal of Pediatric Surgery, (1997) 32/2 (275-282).
Refs: 47
ISSN: 0022-3468 CODEN: JPDSA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
007 Pediatrics and Pediatric Surgery
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
TI The role of inflammatory cytokines and nitric oxide in the pathogenesis of

necrotizing enterocolitis.

AB Purpose: The role of inflammatory cytokines in the pathogenesis of **necrotizing enterocolitis** (NEC) is still undefined. Elevated levels of interleukin (IL)-6 and **tumor necrosis factor** (**TNF**)-.alpha. have been measured in infants with NEC, while elevated levels of nitric oxide (NO) have been reported in **newborn** infants with clinical sepals. However, the cellular source of the NO or cytokines is unknown. The authors hypothesized that local.

CT Medical Descriptors:
*inflammation
***necrotizing enterocolitis**
apical membrane
apoptosis
clinical article
conference paper
controlled study
human
human tissue
intestine cell
intestine resection
intestine villus
jejunostomy
newborn
priority journal
sepsis
*cytokine: EC, endogenous compound
*nitric oxide: EC, endogenous compound
interleukin 6: EC, endogenous compound
messenger rna: EC, endogenous compound
nitric oxide synthase: EC, endogenous compound
peroxynitrite: EC, endogenous compound
transforming growth factor beta: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound

L15 ANSWER 35 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB The role of platelet activating factor (PAF), a potent ulcerogen mediator in the digestive tract, is thought to be important in the genesis of **necrotizing enterocolitis**. The aim of this study was to evaluate the role of PAF in the perpetuation and aggravation of gastrointestinal damage resulting from limited ischemia in the 2-day-old piglet using a natural PAF antagonist (BN 50727). Animals were separated into six groups: U4, controls; S, sham operated animals undergoing laparotomy; I4 and I9, ligation of the mesenteric vessels in the last ileal loop; IT4 and IT9, same procedure together with treatment with BN 50727 (50 mg/kg) orally before and after surgery and intraperitoneally during surgery. Animals were killed at day 4 in groups U4, S, I4 and IT4 and at day 9 in groups I9 and IT9, with histological studies and mediator measurements taken. Macroscopic and histological lesions of intestinal wall in groups I4, I9, IT4 and IT9 were similar to those of human neonatal **necrotizing enterocolitis** and did not vary according to the absence or the presence of BN 50727 treatment (P = .7, I4 v IT4 and P = .9, I9 v IT9). Peritoneal bands were significantly reduced in treated groups IT4 and IT9 as compared with untreated ones I4 and I9 (P = .003). Mucosal PAF levels in the terminal ileum were higher in group I4 than in groups U4 or I4. In the upper loop, mucosal PAF levels were comparable in all groups. An increase in stool PAF levels was observed only in group I9 (26.4 ng/g v 4.7 ng/g, I9 v U4 + S, P < .05), whereas values comparable to

those observed in controls were detected in other groups (I4, 7.2 ng/g; IT4, 4.5 ng/g; IT9, 6.8 ng/g). **Tumor necrosis factor** alpha (**TNF**.alpha.) measurements did not exhibit any difference between groups. Using a PAF antagonist, the role of PAF in the aggravation of intestinal damage after ischemia was not remarkable because treatment did not induce any modifications of parietal intestinal lesions. PAF antagonists appeared to reduce significantly the local peritoneal consequences of local inflammation.

ACCESSION NUMBER: 97002807 EMBASE
DOCUMENT NUMBER: 1997002807
TITLE: Effect of BN 50727 on pathological findings and tissue platelet activating factor levels during ileal ischemia in **newborn** piglets.
AUTHOR: De Boissieu D.; Canarelli J.P.; Cordonnier C.; Richard S.; Leke A.; Tarrade T.; Postel J.P.; Dupont C.
CORPORATE SOURCE: D. De Boissieu, Hopital Saint Vincent de Paul, 82 Avenue Denfert-Rochereau, 75014 Paris, France
SOURCE: Journal of Pediatric Surgery, (1996) 31/12 (1675-1679). ISSN: 0022-3468 CODEN: JPDSA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

TI Effect of BN 50727 on pathological findings and tissue platelet activating factor levels during ileal ischemia in **newborn** piglets.

AB . . . activating factor (PAF), a potent ulcerogen mediator in the digestive tract, is thought to be important in the genesis of **necrotizing enterocolitis**. The aim of this study was to evaluate the role of PAF in the perpetuation and aggravation of gastrointestinal damage. . . . and histological lesions of intestinal wall in groups I4, I9, IT4 and IT9 were similar to those of human neonatal **necrotizing enterocolitis** and did not vary according to the absence or the presence of BN 50727 treatment (P = .7, I4 v. . . . comparable to those observed in controls were detected in other groups (I4, 7.2 ng/g; IT4, 4.5 ng/g; IT9, 6.8 ng/g). **Tumor necrosis factor** alpha (**TNF**.alpha.) measurements did not exhibit any difference between groups. Using a PAF antagonist, the role of PAF in the aggravation of. . .

CT Medical Descriptors:
*intestine ischemia
***necrotizing enterocolitis**
animal experiment
animal model
animal tissue
article
controlled study
female
histology
inflammation
intestine injury
laparotomy
male
nonhuman
oral drug administration
pathophysiology
priority journal

*bn 50727
*thrombocyte activating factor antagonist
tumor necrosis factor alpha
unclassified drug

L15 ANSWER 36 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AB **Newborn** infants often suffer from bacterial and viral infections without presenting typical symptoms. Therefore, reliable methods for detecting and monitoring sepsis in the **newborn** would be beneficial. In older patients C-reactive protein (CRP) and neopterin have proved useful serum markers of infection and inflammation. Both of these markers are regulated by cytokines, and it has been proposed that cytokines themselves could be used to monitor immune activation and infection. This study has examined the levels of CRP, neopterin, soluble IL-2R, tumour necrosis factor-alpha (**TNF**-.alpha.) and interferon-gamma (IFN-.gamma.) in cord blood samples from both premature and term **neonates**. Having established reference ranges for these analytes, serial measurements were made in babies requiring intensive care support. The results suggest that in preterm infants the simultaneous measurement of CRP and neopterin, and possibly soluble IL-2R, may provide an accurate early diagnosis of sepsis and may be of use in differentiating between bacterial and viral etiologies. In addition, serial measurement of these markers may help in the early diagnosis of **necrotizing enterocolitis** (NEC).
ACCESSION NUMBER: 96275707 EMBASE
DOCUMENT NUMBER: 1996275707
TITLE: Inflammatory and immunological markers in preterm infants: Correlation with disease.
AUTHOR: Jurges E.S.; Henderson D.C.
CORPORATE SOURCE: Department of Immunology, Chelsea and Westminster Hospital, 369 Fulham Road,London SW10 9NH, United Kingdom
SOURCE: Clinical and Experimental Immunology, (1996) 105/3 (551-555).
ISSN: 0009-9104 CODEN: CEXIAL
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
005 General Pathology and Pathological Anatomy
007 Pediatrics and Pediatric Surgery
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Newborn** infants often suffer from bacterial and viral infections without presenting typical symptoms. Therefore, reliable methods for detecting and monitoring sepsis in the **newborn** would be beneficial. In older patients C-reactive protein (CRP) and neopterin have proved useful serum markers of infection and inflammation.. . . to monitor immune activation and infection. This study has examined the levels of CRP, neopterin, soluble IL-2R, tumour necrosis factor-alpha (**TNF**-.alpha.) and interferon-gamma (IFN-.gamma.) in cord blood samples from both premature and term **neonates**. Having established reference ranges for these analytes, serial measurements were made in babies requiring intensive care support. The results suggest. . . differentiating between bacterial and viral etiologies. In addition,

serial measurement of these markers may help in the early diagnosis of **necrotizing enterocolitis** (NEC).

CT Medical Descriptors:
***necrotizing enterocolitis: DI, diagnosis**
*sepsis: DI, diagnosis
article
blood level
clinical article
controlled study
female
human
male
newborn
priority journal
*c reactive protein: EC, endogenous compound
*interleukin 2 receptor: EC, endogenous compound
*neopterin: EC, endogenous compound
***tumor necrosis factor alpha: EC, endogenous compound**

L15 ANSWER 37 OF 50 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 4

AB Increased plasma **tumor necrosis factor** .alpha. (**TNF**) concn. correlates with mortality in sepsis. We suggested that pentoxifylline (PTXF), which is known to inhibit **TNF** prodn., may improve survival and attenuate clin. symptoms of sepsis in **neonates**. Plasma **TNF** levels were evaluated in 29 **newborn** infants with sepsis. Patients were randomly assigned into two groups, receiving PTXF in a dose of 5 mg/kg per h for 6 h or placebo (saline), on 3 successive days. Both groups were subjected to the same conventional therapy. **TNF** was evaluated before and after PTXF or placebo administration on the 1st and 3rd days of therapy. There was a statistically significant decrease in plasma **TNF** level in the PTXF group when the values before the first and after the last PTXF infusion were compared [mean: 671.5 pg/mL; SD: 438; med: 729.6 vs mean: 41.0 pg/mL; SD: 64.1; med: 11.5; P < 0.000004]. In the placebo group, decrease was not significant [mean: 633.0 pg/mL SD: 488.6; med: 618.9 vs 246.9 pg/mL; SD: 243.9; med: 191.0]. A significantly higher plasma **TNF** level, evaluated after the last PTXF infusion, was found in the placebo group [246,9 pg/mL vs 41.0 pg/mL; P < 0.001]. Only one of four infants with signs of shock in the placebo group survived, whereas all of five **newborns** with symptoms of shock in the PTXF group survived [P < 0.04]. An increased incidence of metabolic acidosis [P < 0.05], **necrotizing enterocolitis** [P < 0.04] and renal insufficiency [P < 0.05] was obsd. in infants in the placebo group. PTXF inhibits prodn. of **TNF** and may have therapeutic value in the treatment of premature infants with sepsis complicated by shock.

ACCESSION NUMBER: 1996:292649 CAPLUS
DOCUMENT NUMBER: 125:398
TITLE: Pentoxifylline reduces plasma **tumor necrosis factor**-alpha concentration in premature infants with sepsis
AUTHOR(S): Lauterbach, Ryszard; Zembala, Marek
CORPORATE SOURCE: Department Neonatology, Jagiellonian University Medical College, Krakow, P-31-501, Pol.
SOURCE: European Journal of Pediatrics (1996), 155(5), 404-409
CODEN: EJPEDT; ISSN: 0340-6199
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Pentoxifylline reduces plasma **tumor necrosis**

factor-alpha concentration in premature infants with sepsis

AB Increased plasma **tumor necrosis factor** .alpha. (**TNF**) concn. correlates with mortality in sepsis. We suggested that pentoxifylline (PTXF), which is known to inhibit **TNF** prodn., may improve survival and attenuate clin. symptoms of sepsis in **neonates**. Plasma **TNF** levels were evaluated in 29 **newborn** infants with sepsis. Patients were randomly assigned into two groups, receiving PTXF in a dose of 5 mg/kg per h for 6 h or placebo (saline), on 3 successive days. Both groups were subjected to the same conventional therapy. **TNF** was evaluated before and after PTXF or placebo administration on the 1st and 3rd days of therapy. There was a statistically significant decrease in plasma **TNF** level in the PTXF group when the values before the first and after the last PTXF infusion were compared [mean: 671.5 pg/mL; SD: 438; med: 729.6 vs mean: 41.0 pg/mL; SD: 64.1; med: 11.5; P < 0.000004]. In the placebo group, decrease was not significant [mean: 633.0 pg/mL SD: 488.6; med: 618.9 vs 246.9 pg/mL; SD: 243.9; med: 191.0]. A significantly higher plasma **TNF** level, evaluated after the last PTXF infusion, was found in the placebo group [246,9 pg/mL vs 41.0 pg/mL; P < 0.001]. Only one of four infants with signs of shock in the placebo group survived, whereas all of five **newborns** with symptoms of shock in the PTXF group survived [P < 0.04]. An increased incidence of metabolic acidosis [P < 0.05], **necrotizing enterocolitis** [P < 0.04] and renal insufficiency [P < 0.05] was obsd. in infants in the placebo group. PTXF inhibits prodn. of **TNF** and may have therapeutic value in the treatment of premature infants with sepsis complicated by shock.

ST pentoxifylline **TNF** premature infant sepsis shock

IT Sepsis and Septicemia
(pentoxifylline reduces plasma **TNF**-.alpha. in premature infants with sepsis)

IT Developmental stages
(infant, pentoxifylline reduces plasma **TNF**-.alpha. in premature infants with sepsis)

IT Shock
(septic, pentoxifylline reduces plasma **TNF**-.alpha. in premature infants with sepsis)

IT Lymphokines and Cytokines
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**tumor necrosis factor**-.alpha., pentoxifylline reduces plasma **TNF**-.alpha. in premature infants with sepsis)

IT 6493-05-6, Pentoxifylline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pentoxifylline reduces plasma **TNF**-.alpha. in premature infants with sepsis)

L15 ANSWER 38 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB We have addressed two critical questions concerning NEC development. 1) Why is the neonatal intestine particularly susceptible to necrosis? and 2) Does PAF play a critical role in NEC development? We have found that intestinal tissue of the **newborn** has the highest specific activity for the acetyltransferase of the de novo pathway. It is suggested that the high capacity of this tissue to synthesize PAF may contribute to

the fact that the necrosis of the **newborn** is more prevalent in this tissue. We have previously reported that dexamethasone lowers the activity of acetyl-CoA:lyso-PAF acetyltransferase in liver and spleen. This hormone also cause an increase in plasma PAF-acetylhydrolase activity and an increased secretion of PAF- acetylhydrolase by various macrophages. It would, therefore, appear that the beneficial effects of glucocorticoids on the prevention of NEC may be due to both increased inactivation of PAF as caused by the increase in PAF- acetylhydrolase as well as a decrease in PAF synthesis. We are presently investigating the effect of glucocorticoids on acetyl-CoA: alkyl-lyso-sn- glycero-3-phosphate acetyltransferase. The reported studies in which NEC was prevented by intravenous infusion of recombinant PAF-acetylhydrolase provides further documentation as to the importance of PAF in the development of NEC. The specific activity of PAF-acetylhydrolase required for protection by dexamethasone was similar. This finding would be suggestive of the fact that the mechanisms by which dexamethasone causes a complete protection against NEC may be mediated by increasing the plasma activity. Other mechanisms have been proposed such as facilitating the maturation of the small bowel. As discussed, other factors such as hypoxia, endotoxins, **TNF**.alpha., and enternal feeding have been suggested to be contributing agents of NEC development. Many of these factors and procedures are known to increase in PAF. We have suggested a mechanism to explain the increase in PAF formation as caused LPS, **TNF**.alpha., and interleukins being the inhibition of the secretion of PAF-AH by macrophages. Our previous reports on the mechanisms involve in the prevention of NEC by glucocorticoids and the reported findings that human recombinant PAF-acetylhydrolase can prevent NEC provide further support for a central role for PAF in NEC development. Furthermore, the presence of a high PAF biosynthetic activity in the neonatal intestine affords an explanation as to why this tissue is highly susceptible to this disease.

ACCESSION NUMBER: 97316303 EMBASE
DOCUMENT NUMBER: 1997316303
TITLE: The central ~~role of PAF in~~ **necrotizing enterocolitis** ~~development~~.
AUTHOR: Muguruma K.; Gray P.W.; Tjoelker L.W.; Johnston J.M.
CORPORATE SOURCE: K. Muguruma, Department of Biochemistry, CHIGCRBS, Texas Univ. Southwestern Med. Ctr., 5323 Harry Hines Boulevard, Dallas, TX 75235-9051, United States
SOURCE: Advances in Experimental Medicine and Biology, (1996) 407/- (379-382).
Refs: 13
ISSN: 0065-2598 CODEN: AEMBAP
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
TI The central role of PAF in **necrotizing enterocolitis** development.
AB . . . necrosis? and 2) Does PAF play a critical role in NEC development? We have found that intestinal tissue of the **newborn**

has the highest specific activity for the acetyltransferase of the de novo
pathway. It is suggested that the high capacity of this tissue to synthesize PAF may contribute to the fact that the necrosis of the **newborn** is more prevalent in this tissue. We have previously reported that dexamethasone lowers the activity of acetyl-CoA:lyso-PAF acetyltransferase in liver. . . have been proposed such as facilitating
the maturation of the small bowel. As discussed, other factors such as hypoxia, endotoxins, **TNF**.alpha., and enternal feeding have been suggested to be contributing agents of NEC development. Many of these factors and procedures are. . . known to increase in PAF. We have suggested a mechanism to explain the increase in PAF formation as caused LPS, **TNF**.alpha., and interleukins being the inhibition of the secretion of PAF-AH by macrophages. Our previous reports on the mechanisms
involve in. . .

CT Medical Descriptors:
***necrotizing enterocolitis: ET, etiology**
***necrotizing enterocolitis: DT, drug therapy**
***necrotizing enterocolitis: PC, prevention**
animal cell
animal tissue
conference paper
controlled study
disease predisposition
enzyme activity
enzyme synthesis
fetus
kidney
liver
microsome
newborn
nonhuman
priority journal
rat
small intestine
*1 alkyl 2 acetylglycerophosphocholine esterase: DV, drug development
*1 alkyl 2 acetylglycerophosphocholine esterase: DT, drug therapy
*1 alkyl 2 acetylglycerophosphocholine. . .

L15 ANSWER 39 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB The role of inflammatory cytokines in the pathogenesis of neurological disorders is not entirely clear. The neurotoxic effects of cytokines, and perhaps indirectly bacterial endotoxins, could be mediated by the stimulation of immunocompetent cells in the brain to produce toxic concentrations of nitric oxide (NO) and reactive nitrogen oxides. NO is a short-lived, diffusible molecule that has a variety of biological activities including vasorelaxation, neurotransmission, and cytotoxicity. Both constitutive and inducible NO synthase has been described in astrocytes in vitro. Here we demonstrate that **newborn** mouse cortical astrocytes, when coincubated with neonatal mouse cerebellar granule cells or hippocampal neurons, induced neurotoxicity upon stimulation with endotoxin (lipopolysaccharide) (ED50 30 ng/ml). Astrocytes were unresponsive to the cytokines **tumor necrosis factor**-.alpha. or interleukin-1.beta. individually, but exhibited a marked synergistic stimulation in their combined presence. Moreover, meningeal fibroblasts treated with **tumor necrosis factor**-.alpha., but not interleukin-1.beta. or lipopolysaccharide, elaborated neurotoxicity for

cocultured granule cells (ED50 30 U/ml). In cocultures of immunostimulated astrocytes or meningeal fibroblasts, neurotoxicity was blocked by the NO synthase inhibitors N(.omega.)-nitro-L- arginine and N(.omega.)-nitro-D-arginine methyl ester, and by oxyhemoglobin, which inactivates NO. Astroglial-induced neurotoxicity was not affected by N-methyl-D-aspartate receptor antagonists. Superoxide dismutase, which de- grades superoxide anion, attenuated astrocyte- and fibroblast-mediated neurotoxicity, indicating that endogenous superoxide anion may react with NO to form toxic peroxynitrite and its breakdown products. These findings suggest a potentially important role for glial- and meningeal fibroblast- induced NO synthase in the pathophysiology of CNS disease states of immune or inflammatory origin.

ACCESSION NUMBER: 95002818 EMBASE
DOCUMENT NUMBER: 1995002818
TITLE: Inflammatory mediator stimulation of astrocytes and meningeal fibroblasts induces neuronal degeneration via the nitridergic pathway.
AUTHOR: Skaper S.D.; Facci L.; Leon A.
CORPORATE SOURCE: Researchlife S.c.p.A., Centro di Ricerca Biomedica, Ospedale Civile,31033 Castelfranco Veneto (TV), Italy
SOURCE: Journal of Neurochemistry, (1995) 64/1 (266-276).
ISSN: 0022-3042 CODEN: JONRA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
AB . . . neurotransmission, and cytotoxicity. Both constitutive and inducible NO synthase has been described in astrocytes in vitro. Here we demonstrate that **newborn** mouse cortical astrocytes, when coincubated with neonatal mouse cerebellar granule cells or hippocampal neurons, induced neurotoxicity upon stimulation with endotoxin (lipopolysaccharide) (ED50 30 ng/ml). Astrocytes were unresponsive to the cytokines **tumor necrosis factor**-.alpha. or interleukin-1.beta. individually, but exhibited a marked synergistic stimulation in their combined presence. Moreover, meningeal fibroblasts treated with **tumor necrosis factor**-.alpha., but not interleukin-1.beta. or lipopolysaccharide, elaborated neurotoxicity for cocultured granule cells (ED50 30 U/ml). In cocultures of immunostimulated astrocytes or. . .
CT Medical Descriptors:
*astrocyte
*inflammation: ET, etiology
*nerve degeneration: ET, etiology
*neurotoxicity: ET, etiology
animal cell
article
cerebellum
controlled study
fibroblast
glia
granule cell
hippocampus
meninx
mouse

nerve cell lesion: ET, etiology
nerve cell necrosis: ET, etiology
newborn
nonhuman
priority journal
rat
*cytokine
*endotoxin
*nitric oxide: EC, endogenous compound
*nitric oxide synthase: EC, endogenous compound
*nitrogen oxide: EC, endogenous compound
interleukin 1beta
lipopolysaccharide
n methyl dextro aspartic acid receptor blocking agent
n(g) nitroarginine
n(g) nitroarginine methyl ester
oxyhemoglobin
superoxide: EC, endogenous compound
superoxide dismutase
tumor necrosis factor alpha

L15 ANSWER 40 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB Macrophages have been found to release glutamate and thereby induce neuronal cell death by excitotoxicity, a mechanism that seems to be operative in various neurologic diseases. In this study, it is shown that the presence of both cystine and glutamine in the culture medium is indispensable for brain macrophages to release glutamate and to cause neuronal cell death. Furthermore, release of glutamate requires protein synthesis since cycloheximide prevented accumulation of the neurotoxic molecule in supernatants of microglial cell cultures. Aminoadipate, which was shown to inhibit the uptake of cystine by system x(c)/- in fibroblasts, efficiently reduced the release of glutamate. The requirement of glutamine and cystine for the release of glutamate by microglial cells as well as the inhibitory effect observed with aminoadipate shows the transport system x(c)/- to be essential for the release of the excitotoxin glutamate by microglial cells. Phagocytosis of zymosan particles and stimulation with different bacterial components, such as LPS, protein A, tuberculin, and Staphylococcus enterotoxin A increased glutamate release two- to threefold above basal values. In addition, the effect of bacterial components was mimicked by **TNF**- .alpha., but not by IL-1 and IL-6. Cytokines known to deactivate macrophages, such as TGF-.beta., IL-4, and IL-10, did not affect the transport system x(c)/- in microglial cells. However, dexamethasone suppressed the glutamate release up to 50%.

ACCESSION NUMBER: 94102663 EMBASE
DOCUMENT NUMBER: 1994102663
TITLE: Involvement of the cystine transport system x(c)/- in the macrophage- induced glutamate-dependent cytotoxicity to neurons.
AUTHOR: Piani D.; Fontana A.
CORPORATE SOURCE: Section of Clinical Immunology, University Hospital, Haldeliweg 4,CH-8044 Zurich, Switzerland
SOURCE: Journal of Immunology, (1994) 152/7 (3578-3585).
ISSN: 0022-1767 CODEN: JOIMA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
AB . . . A increased glutamate release two- to threefold above basal values. In addition, the effect of bacterial components was mimicked by **TNF**- .alpha., but not by IL-1 and IL-6. Cytokines known to deactivate macrophages, such as TGF-.beta., IL-4, and IL-10, did not. .
.
CT Medical Descriptors:
***nerve cell necrosis**
amino acid transport
animal cell
article
controlled study
cytotoxicity
female
fibroblast
macrophage
male
microglia
mouse
nerve cell culture
newborn
nonhuman
phagocytosis
priority journal
protein synthesis
*cystine
*glutamic acid: EC, endogenous compound
*glutamine
aminoadipic acid
cycloheximide
dexamethasone
interleukin 1
interleukin 10
interleukin 4
interleukin 6
lipopolysaccharide
protein a
staphylococcus enterotoxin a
transforming growth factor beta
tuberculin
tumor necrosis factor alpha
zymosan

L15 ANSWER 41 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AB We hypothesized that plasma levels of cytokines such as interleukin-6 and **tumor necrosis factor** (**TNF**) are elevated in critically ill infants with sepsis and **necrotizing enterocolitis** (NEC) and that the magnitude of their elevation is correlated with mortality rate. We measured plasma levels of interleukin-6 and **TNF** in 62 **newborn** infants with suspected sepsis or NEC. Eighteen infants had bacterial sepsis, 9 had bacterial sepsis plus NEC, and 15 had NEC but negative culture results. Twenty comparably ill infants with negative results on culture of systemic specimens served as study control subjects. Interleukin-6 levels were five- to tenfold higher infants with bacterial sepsis plus NEC at the onset of disease than in

infants with bacterial sepsis alone, in infants with NEC but negative culture results, and in control infants ($p < 0.01$). These differences persisted throughout the 48-hour study period. Interleukin-6 levels were also significantly higher in nonsurvivors than in survivors ($p < 0.001$). In contrast, plasma **TNF** values were not consistently increased in any of the groups. We conclude that plasma interleukin-6 is a more reliable indicator of bacterial sepsis and NEC than plasma **TNF** and may identify infants who might benefit from immunotherapeutic strategies.

ACCESSION NUMBER: 94028422 EMBASE
DOCUMENT NUMBER: 1994028422
TITLE: Cytokine elevations in critically ill infants with sepsis and **necrotizing enterocolitis**.
AUTHOR: Harris M.C.; Costarino Jr. A.T.; Sullivan J.S.; Dulkerian S.; McCawley L.; Corcoran L.; Butler S.; Kilpatrick L.
CORPORATE SOURCE: Division of Neonatology, Children's Hospital of Philadelphia, 34th Street/Civic Center Boulevard,Philadelphia, PA 19104, United States
SOURCE: Journal of Pediatrics, (1994) 124/1 (105-111).
ISSN: 0022-3476 CODEN: JOPDAB
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
007 Pediatrics and Pediatric Surgery
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

TI Cytokine elevations in critically ill infants with sepsis and **necrotizing enterocolitis**.

AB We hypothesized that plasma levels of cytokines such as interleukin-6 and **tumor necrosis factor** (**TNF**) are elevated in critically ill infants with sepsis and **necrotizing enterocolitis** (NEC) and that the magnitude of their elevation is correlated with mortality rate. We measured plasma levels of interleukin-6 and **TNF** in 62 **newborn** infants with suspected sepsis or NEC. Eighteen infants had bacterial sepsis, 9 had bacterial sepsis plus NEC, and 15 had. . . 48-hour study period. Interleukin-6 levels were also significantly higher in nonsurvivors than in survivors ($p < 0.001$). In contrast, plasma **TNF** values were not consistently increased in any of the groups. We conclude that plasma interleukin-6 is a more reliable indicator of bacterial sepsis and NEC than plasma **TNF** and may identify infants who might benefit from immunotherapeutic strategies.

CT Medical Descriptors:
*infant mortality
***newborn sepsis: DI, diagnosis**
***newborn sepsis: ET, etiology**
*sepsis: DI, diagnosis
*sepsis: ET, etiology
article
bacterial infection
clinical trial
controlled study
human
mortality
priority journal
*cytokine: EC, endogenous compound
*interleukin 6: EC, endogenous compound
***tumor necrosis factor: EC, endogenous compound**

L15 ANSWER 42 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB Ascites fluid was obtained intraoperatively in 12 consecutively treated **neonates** (6M, 6F, mean weight 940 g, mean gestational age 27th week, lethality 3/12) suffering from **necrotizing enterocolitis** (NEC). The concentrations of endotoxin and cytokines (IL-1, IL-6, **TNF**) were determined. Endotoxin and interleukins were excessively elevated in all patients, **TNF** only in those who survived. Postoperative treatment included the use of a continuous abdominal lavage system. This therapeutical procedure allows the elimination of endotoxin and cytokines out of the abdominal cavity in order to reduce their adverse biological effect.

ACCESSION NUMBER: 94186019 EMBASE
DOCUMENT NUMBER: 1994186019
TITLE: Is the elimination of endotoxin and cytokines with continuous lavage an alternative procedure in **necrotizing enterocolitis**?.
AUTHOR: Birk D.; Berger D.; Limmer J.; Beger H.G.
CORPORATE SOURCE: Department of General Surgery, University Ulm, Steinhovelstrasse 9,D-89075 Ulm, Germany
SOURCE: Acta Paediatrica, International Journal of Paediatrics, Supplement, (1994) 83/396 (24-26).
ISSN: 0803-5326 CODEN: APUPEI
COUNTRY: Norway
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

TI Is the elimination of endotoxin and cytokines with continuous lavage an alternative procedure in **necrotizing enterocolitis**?.

AB Ascites fluid was obtained intraoperatively in 12 consecutively treated **neonates** (6M, 6F, mean weight 940 g, mean gestational age 27th week, lethality 3/12) suffering from **necrotizing enterocolitis** (NEC). The concentrations of endotoxin and cytokines (IL-1, IL-6, **TNF**) were determined. Endotoxin and interleukins were excessively elevated in all patients, **TNF** only in those who survived. Postoperative treatment included the use of a continuous abdominal lavage system. This therapeutical procedure allows. . .

CT Medical Descriptors:
***necrotizing enteritis: TH, therapy**
*peritoneum lavage
ascites
clinical article
conference paper
female
human
male
newborn
postoperative period
priority journal
*cytokine: EC, endogenous compound
*endotoxin: EC, endogenous compound
interleukin 1: EC, endogenous compound
interleukin 6: EC, endogenous compound
tumor necrosis factor: EC, endogenous compound

L15 ANSWER 43 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB Plasma concentrations of tumour necrosis factor (**TNF**) and interleukin-6 (IL-6) were measured by ELISA in samples taken from 24

infants with **necrotizing enterocolitis** (NEC) between 0 and 306 h from diagnosis. **TNF** was detected (> 10 pg/ml) in 71% samples with a mean of 48 pg/ml (95% CI 42 to 55 pg/ml) and did not vary with either time from diagnosis or severity of disease. IL-6 was raised during the first 48 h with a significant difference between stage II (mean 127 pg/ml, 95% CI 10 to 329 pg/ml) and stage III (mean 3127 pg/ml, 95% CI 1809 to 4445 pg/ml, p = 0.001). Postoperative plasma IL-6 concentration fell to similar levels seen in stage II (mean 150 pg/ml, 95% CI 37 to 283 pg/ml, p = 0.79). We conclude that plasma concentration of IL-6 rather than **TNF** reflects the clinical severity of **necrotizing enterocolitis** and that the relative level of these cytokines has important implications for the use of anti-cytokine therapy in NEC.

ACCESSION NUMBER: 94186017 EMBASE
DOCUMENT NUMBER: 1994186017
TITLE: Plasma cytokine levels in **necrotizing enterocolitis**.
AUTHOR: Morecroft J.A.; Spitz L.; Hamilton P.A.; Holmes S.J.K.
CORPORATE SOURCE: Department of Surgery, Institute of Child Health, 30 Guilford Street,London WC1N 1EH, United Kingdom
SOURCE: Acta Paediatrica, International Journal of Paediatrics, Supplement, (1994) 83/396 (18-20).
ISSN: 0803-5326 CODEN: APUPEI
COUNTRY: Norway
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
026 Immunology, Serology and Transplantation
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

TI Plasma cytokine levels in **necrotizing enterocolitis**.

AB Plasma concentrations of tumour necrosis factor (**TNF**) and interleukin-6 (IL-6) were measured by ELISA in samples taken from 24 infants with **necrotizing enterocolitis** (NEC) between 0 and 306 h from diagnosis. **TNF** was detected (> 10 pg/ml) in 71% samples with a mean of 48 pg/ml (95% CI 42 to 55 pg/ml). . . 150 pg/ml, 95% CI 37 to 283 pg/ml, p = 0.79). We conclude that plasma concentration of IL-6 rather than **TNF** reflects the clinical severity of **necrotizing enterocolitis** and that the relative level of these cytokines has important implications for the use of anti-cytokine therapy in NEC.

CT Medical Descriptors:
***necrotizing enteritis**
clinical article
conference paper
disease severity
enzyme linked immunosorbent assay
human
newborn
priority journal
marker
*cytokine: EC, endogenous compound
interleukin 6: EC, endogenous compound
tumor necrosis factor: EC, endogenous compound

L15 ANSWER 44 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB **Tumor necrosis factor**-.alpha. (**TNF**) has been shown to induce intestinal necrosis in animals. Moreover, plasma **TNF** levels are elevated in patients with

necrotizing enterocolitis. Thus, it is possible that **TNF** plays a role in the pathogenesis of NEC. In the present study we used in situ hybridization (with human **TNF** riboprobes) to localize **TNF** transcripts in the intestinal tissues from normal biopsies and NEC patients. We found that in normal intestine a small amount of **TNF** mRNA was present only in Paneth cells. In contrast, in the acute stage of NEC, a high amount of **TNF** transcripts was detected in Paneth cells as well as in infiltrating eosinophils. In one case that showed infiltrating macrophages, **TNF** mRNA was also detected in these cells. Resident macrophages in the lamina propria and other inflammatory cells were negative for **TNF** transcripts. Our results suggest that: 1) Paneth cells are the major source of **TNF** transcripts in normal intestine, and 2) there is a marked increase in **TNF** mRNA formation in Paneth cells, as well as in infiltrating eosinophils and macrophages in patients with NEC. **TNF**- containing cells may play an important role in the pathophysiology of NEC.

ACCESSION NUMBER: 94062306 EMBASE
DOCUMENT NUMBER: 1994062306
TITLE: Cellular localization of **tumor necrosis factor** (**TNF**)-.alpha. transcripts in normal bowel and in **necrotizing enterocolitis**.
AUTHOR: Tan X.; Hsueh W.; Gonzalez-Crussi F.
CORPORATE SOURCE: Department of Pathology, Children's Memorial Hospital, 2300 Children's Plaza,Chicago, IL 60614, United States
SOURCE: American Journal of Pathology, (1993) 142/6 (1858-1865). ISSN: 0002-9440 CODEN: AJPAA4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
007 Pediatrics and Pediatric Surgery
029 Clinical Biochemistry
048 Gastroenterology
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English

TI Cellular localization of **tumor necrosis factor** (**TNF**)-.alpha. transcripts in normal bowel and in **necrotizing enterocolitis**.

AB **Tumor necrosis factor**-.alpha. (**TNF**) has been shown to induce intestinal necrosis in animals. Moreover, plasma **TNF** levels are elevated in patients with **necrotizing enterocolitis**. Thus, it is possible that **TNF** plays a role in the pathogenesis of NEC. In the present study we used in situ hybridization (with human **TNF** riboprobes) to localize **TNF** transcripts in the intestinal tissues from normal biopsies and NEC patients. We found that in normal intestine a small amount of **TNF** mRNA was present only in Paneth cells. In contrast, in the acute stage of NEC, a high amount of **TNF** transcripts was detected in Paneth cells as well as in infiltrating eosinophils. In one case that showed infiltrating macrophages, **TNF** mRNA was also detected in these cells. Resident macrophages in the lamina propria and other inflammatory cells were negative for **TNF** transcripts. Our results suggest that: 1) Paneth cells are the major source of **TNF** transcripts in normal intestine, and 2) there is a marked increase in **TNF** mRNA formation in Paneth cells, as well as in infiltrating eosinophils and macrophages in patients with NEC. **TNF**- containing cells may play an important role in the

pathophysiology of NEC.
CT Medical Descriptors:
*eosinophil
*gene
*macrophage
***necrotizing enterocolitis: DI, diagnosis**
***necrotizing enterocolitis: ET, etiology**
*paneth cell
article
cellular distribution
clinical article
controlled study
female
gene expression
histology
human
human tissue
immunohistochemistry
in situ hybridization
intestine
male
newborn
priority journal
*messenger rna: EC, endogenous compound
***tumor necrosis factor alpha: EC, endogenous compound**
complementary dna: EC, endogenous compound

L15 ANSWER 45 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92368181 EMBASE
DOCUMENT NUMBER: 1992368181
TITLE: Varicella-zoster contracted in the second trimester of pregnancy.
AUTHOR: Michie C.A.; Acolet D.; Charlton R.; Stevens J.P.; Happerfield L.C.; Bobrow L.G.; Kangro H.; Gau G.; Modi N.
CORPORATE SOURCE: Paediatrics/Neonatal Medicine Dept., Royal Postgraduate Medical School, Queen Charlotte's/Chelsea Hospital,London W6 OXG, United Kingdom
SOURCE: Pediatric Infectious Disease Journal, (1992) 11/12 (1050-1053).
ISSN: 0891-3668 CODEN: PIDJEV
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
005 General Pathology and Pathological Anatomy
007 Pediatrics and Pediatric Surgery
037 Drug Literature Index
LANGUAGE: English
CT Medical Descriptors:
*chickenpox: CN, congenital disorder
*chickenpox: DI, diagnosis
*chickenpox: DT, drug therapy
*chickenpox: ET, etiology
*second trimester pregnancy
*varicella zoster virus
article
case report
clinical feature
human
immune response
immunohistochemistry

in situ hybridization
intravenous drug administration
male
necrosis: DI, diagnosis
newborn
perinatal infection: ET, etiology
perinatal infection: DT, drug therapy
perinatal infection: DI, diagnosis
perinatal infection: CN, congenital disorder
priority journal
radioimmunoassay
serology
virus culture
virus transmission
*aciclovir: AD, drug. . . AD, drug administration
*immunoglobulin: CB, drug combination
*immunoglobulin: DT, drug therapy
antibiotic agent: AD, drug administration
antibiotic agent: CB, drug combination
antibiotic agent: DT, drug therapy
tumor necrosis factor alpha: EC, endogenous compound
virus dna
virus protein

L15 ANSWER 46 OF 50 CAPLUS COPYRIGHT 2002 ACS
AB Intravascular platelet-activating factor (PAF) causes ischemic bowel necrosis in rats morphol. similar to neonatal **necrotizing enterocolitis** (NEC). Because endotoxin (LPS) and hypoxia are risk factors for NEC, the authors studied their effect on PAF metab. and the development of intestinal injury. Young male Sprague-Dawley rats were anesthetized with pentobarbital and divided into six exptl. groups: (1) control, (2) LPS alone (2 mg/kg), (3) hypoxia alone (5% O2), (4) LPS + hypoxia, (5) WEB 2086 (PAF antagonist) + LPS + hypoxia, and (6) SRI 63-441
(PAF antagonist) + LPS + hypoxia. Evaluations included blood pressure recording, superior mesenteric artery blood flow, arterial blood gas, white blood cell count, hematocrit, plasma PAF, plasma acetylhydrolase, plasma **tumor necrosis factor**, intestinal
perfusion, and intestinal injury at 3 h. LPS + hypoxia synergistically contributed to hypotension metabolic acidosis hemoconcn., decreased superior mesenteric artery blood flow and intestinal injury. The morbidities resulting from LPS + hypoxia were partially or completely prevented by PAF antagonists. In addn., animals treated with LPS + hypoxia had neutropenia, elevated plasma acetylhydrolase, and elevated plasma **TNF**. Apparently, endogenous PAF may contribute to LPS + hypoxia-induced intestinal hypoperfusion and necrosis.
ACCESSION NUMBER: 1992:445947 CAPLUS
DOCUMENT NUMBER: 117:45947
TITLE: Endotoxin and hypoxia-induced intestinal necrosis in rats: the role of platelet activating factor
AUTHOR(S): Caplan, Michael S.; Kelly, Anne; Hsueh, Wei
CORPORATE SOURCE: Dep. Pediatr., Evanston Hosp., Evanston, IL, 60201, USA
SOURCE: Pediatr. Res. (1992), 31(5), 428-34
CODEN: PEREBL; ISSN: 0031-3998
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Intravascular platelet-activating factor (PAF) causes ischemic bowel necrosis in rats morphol. similar to neonatal **necrotizing enterocolitis** (NEC). Because endotoxin (LPS) and hypoxia are risk

factors for NEC, the authors studied their effect on PAF metab. and the development of intestinal injury. Young male Sprague-Dawley rats were anesthetized with pentobarbital and divided into six exptl. groups: (1) control, (2) LPS alone (2 mg/kg), (3) hypoxia alone (5% O2), (4) LPS + hypoxia, (5) WEB 2086 (PAF antagonist) + LPS + hypoxia, and (6) SRI 63-441 (PAF antagonist) + LPS + hypoxia. Evaluations included blood pressure recording, superior mesenteric artery blood flow, arterial blood gas, white blood cell count, hematocrit, plasma PAF, plasma acetylhydrolase, plasma **tumor necrosis factor**, intestinal perfusion, and intestinal injury at 3 h. LPS + hypoxia synergistically contributed to hypotension metabolic acidosis hemoconcn., decreased superior mesenteric artery blood flow and intestinal injury. The morbidities resulting from LPS + hypoxia were partially or completely prevented by PAF antagonists. In addn., animals treated with LPS + hypoxia had neutropenia, elevated plasma acetylhydrolase, and elevated plasma **TNF**. Apparently, endogenous PAF may contribute to LPS + hypoxia-induced intestinal hypoperfusion and necrosis.

ST neonatal **necrotizing enterocolitis** platelet activating factor

IT Hypoxia
(neonatal **necrotizing enterocolitis** induction by endotoxin and, platelet-activating factor contribution to)

IT Lipopolysaccharides
RL: BIOL (Biological study)
(neonatal **necrotizing enterocolitis** induction by hypoxia and, platelet-activating factor contribution to)

IT Toxins
RL: BIOL (Biological study)
(endo-, neonatal **necrotizing enterocolitis** induction by hypoxia and, platelet-activating factor contribution to)

IT **Newborn**
(premature, **necrotizing enterocolitis** in, endotoxin and hypoxia-induced, platelet-activating factor contribution to)

IT Lymphokines and Cytokines
RL: BIOL (Biological study)
(**tumor necrosis factor**, in endotoxin and hypoxia-induced neonatal **necrotizing enterocolitis**)

IT 65154-06-5, Platelet-activating factor 76901-00-3, Acetylhydrolase
RL: BIOL (Biological study)
(in endotoxin and hypoxia-induced neonatal **necrotizing enterocolitis**)

L15 ANSWER 47 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB **Necrotizing enterocolitis** (NEC) is an important neonatal disease with a high mortality rate. The pathophysiology is unclear but epidemiologic studies suggest that hypoxia and infection are important risk factors. In this review we discuss the effect of hypoxia and platelet-activating factor (PAF) on intestinal blood flow and intestinal necrosis, and implicate PAF as an important mediator in hypoxia-induced intestinal injury. Finally we provide evidence that PAF may be important in neonatal NEC.

ACCESSION NUMBER: 92032690 EMBASE
DOCUMENT NUMBER: 1992032690
TITLE: Hypoxia, PAF, and **necrotizing enterocolitis**.
AUTHOR: Caplan M.S.; Sun X.-M.; Hsueh W.
CORPORATE SOURCE: Department of Pediatrics, Children's Memorial Hospital, Northwestern Univ. Med. Sch.,Chicago, IL 60614, United States

SOURCE: Lipids, (1991) 26/12 (1340-1343).
ISSN: 0024-4201 CODEN: LPDSAP
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
007 Pediatrics and Pediatric Surgery
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
TI Hypoxia, PAF, and **necrotizing enterocolitis**.
AB **Necrotizing enterocolitis** (NEC) is an important neonatal disease with a high mortality rate. The pathophysiology is unclear but epidemiologic studies suggest that. . .
CT Medical Descriptors:
*hypoxia
*intestine blood flow
***intestine necrosis: ET, etiology**
***necrotizing enterocolitis: ET, etiology**
arterial gas
conference paper
human
intestine injury: DT, drug therapy
intestine injury: ET, etiology
intestine ischemia: ET, etiology
newborn
nonhuman
priority journal
*1 [2 [[5 (n octadecylcarbamoyloxymethyl)tetrahydrofurfuryloxy]hydroxyphosphinyloxy]ethyl]quinolinium: DT, drug therapy
*apafant: DT, drug therapy
*hydrolase: EC, endogenous compound
*thrombocyte activating factor
*thrombocyte activating factor antagonist: DT, drug therapy
bacterium lipopolysaccharide
phospholipase a2
tumor necrosis factor

L15 ANSWER 48 OF 50 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 5
AB Because previous investigations have suggested that platelet activating factor and **tumor necrosis factor**-.alpha. (**TNF**-.alpha.) are important mediators of exptl. **necrotizing enterocolitis** in the rat, the authors measured platelet activating factor, acetylhydrolase (the platelet activating factor breakdown enzyme), and **TNF**-.alpha. in the plasma of 12 human **neonates** with **necrotizing enterocolitis** and eight age-matched control subjects with similar gestational ages, postnatal ages, and wts. Almost all patients with **necrotizing enterocolitis** had elevated plasma platelet activating factor values (18.1 ng/mL vs. 3.1 ng/mL in control subjects). Plasma acetylhydrolase activity was lower in patients than in control subjects (10.6 nmol/mL/min vs. 23.0 nmol/mL/min). Plasma **TNF**-.alpha. concn. was significantly elevated in patients with **necrotizing enterocolitis** (136 U/mL vs. 1.5 U/mL), although the individual variation was high. There was no correlation between individual **TNF**-.alpha. and platelet activating factor levels. Thus, platelet activating factor and **TNF**-.alpha. are elevated in patients with **necrotizing**

enterocolitis and suppressed platelet activating factor degrdn. contributes to the increased platelet activating factor levels; platelet activating factor and **TNF**-.alpha. may contribute to the pathophysiol. of **necrotizing enterocolitis**.

ACCESSION NUMBER: 1990:513184 CAPLUS
DOCUMENT NUMBER: 113:113184
TITLE: Role of platelet activating factor and **tumor necrosis factor**-alpha in neonatal **necrotizing enterocolitis**
AUTHOR(S): Caplan, Michael S.; Sun, Xiao Ming; Hsueh, Wei; Hageman, Joseph R.
CORPORATE SOURCE: Dep. Pediatrics Pathol., Child. Mem. Hosp., Chicago, IL, USA
SOURCE: J. Pediatr. (St. Louis) (1990), 116(6), 960-4
CODEN: JOPDAB; ISSN: 0022-3476
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Role of platelet activating factor and **tumor necrosis factor**-alpha in neonatal **necrotizing enterocolitis**

AB Because previous investigations have suggested that platelet activating factor and **tumor necrosis factor**-.alpha. (**TNF**-.alpha.) are important mediators of exptl. **necrotizing enterocolitis** in the rat, the authors measured platelet activating factor, acetylhydrolase (the platelet activating factor breakdown enzyme), and **TNF**-.alpha. in the plasma of 12 human **neonates** with **necrotizing enterocolitis** and eight age-matched control subjects with similar gestational ages, postnatal ages, and wts. Almost all patients with **necrotizing enterocolitis** had elevated plasma platelet activating factor values (18.1 ng/mL vs. 3.1 ng/mL in control subjects). Plasma acetylhydrolase activity was lower in patients than in control subjects (10.6 nmol/mL/min vs. 23.0 nmol/mL/min). Plasma **TNF**-.alpha. concn. was significantly elevated in patients with **necrotizing enterocolitis** (136 U/mL vs. 1.5 U/mL), although the individual variation was high. There was no correlation between individual **TNF**-.alpha. and platelet activating factor levels. Thus, platelet activating factor and **TNF**-.alpha. are elevated in patients with **necrotizing enterocolitis** and suppressed platelet activating factor degrdn. contributes to the increased platelet activating factor levels; platelet activating factor and **TNF**-.alpha. may contribute to the pathophysiol. of **necrotizing enterocolitis**.

ST **tumor necrosis factor neonate necrotizing enterocolitis**; platelet activating factor **neonate necrotizing enterocolitis**

IT **Newborn**
(platelet-activating factor and **tumor necrosis factor**-.alpha. of blood plasma of human, in **necrotizing enterocolitis**)

IT Blood plasma
(**tumor necrosis factor**-.alpha. of, of human **neonates**, in **necrotizing enterocolitis**)

IT Intestine, disease or disorder
(pseudomembranous enterocolitis, pathophysiol. of, platelet-activating factor and **tumor necrosis factor**-.alpha. of blood plasma in, of human **neonates**)

IT Lymphokines and Cytokines

RL: BIOL (Biological study)
(**tumor necrosis factor**-.alpha., of blood plasma, of human **neonates**, in **necrotizing enterocolitis**)

IT 65154-06-5, Blood platelet-activating factor
RL: BIOL (Biological study)
(of blood plasma, of human **neonates**, in **necrotizing enterocolitis**)

L15 ANSWER 49 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB The effect of **tumor necrosis factor** (**TNF**) on expression of major histocompatibility complex (MHC) antigens was examined in mouse glial cells in vitro. **TNF** induced MHC class I, but not class II, antigen expression on the surface of astrocytes but not on oligodendrocytes. Glial cells do not normally express detectable amounts of MHC antigens. Thus **TNF** may play a role in immunopathogenesis of neurologic diseases that involve MHC class I-restricted reactions.

ACCESSION NUMBER: 88120450 EMBASE
DOCUMENT NUMBER: 1988120450
TITLE: **Tumor necrosis factor** induces expression of MHC class I antigens on mouse astrocytes.
AUTHOR: Lavi E.; Suzumura A.; Murasko D.M.; Murray E.M.; Silberberg D.H.; Weiss S.R.
CORPORATE SOURCE: Department of Microbiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, United States
SOURCE: Journal of Neuroimmunology, (1988) 18/3 (245-253). ISSN: 0165-5728 CODEN: JNRIDW
COUNTRY: Netherlands
DOCUMENT TYPE: Journal
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

TI **Tumor necrosis factor** induces expression of MHC class I antigens on mouse astrocytes.

AB The effect of **tumor necrosis factor** (**TNF**) on expression of major histocompatibility complex (MHC) antigens was examined in mouse glial cells in vitro. **TNF** induced MHC class I, but not class II, antigen expression on the surface of astrocytes but not on oligodendrocytes. Glial cells do not normally express detectable amounts of MHC antigens. Thus **TNF** may play a role in immunopathogenesis of neurologic diseases that involve MHC class I-restricted reactions.

CT Medical Descriptors:
*astrocyte
*glia cell
*major histocompatibility complex
***tumor necrosis**
histochemistry
histology
mouse
newborn
priority journal
nonhuman
diagnosis
*gamma interferon

***tumor necrosis factor: PD, pharmacology**

L15 ANSWER 50 OF 50 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AB **Newborn** Swiss and A2G mice were given daily subcutaneous injections for 1 week of highly purified recombinant mouse **tumor necrosis factor** (**TNF**) or mouse interferon .alpha./.beta.. Both treatments resulted in inhibition of growth of suckling mice and severe fatty changes and necrosis in the liver. The simultaneous injection of polyclonal antibody to interferon .alpha./.beta. abrogated the effects of interferon but did not block the effects induced by **TNF**. The kidneys of **TNF**-treated suckling mice could be distinguished from interferon-treated mice by the absence of glomerular basement membrane abnormalities and the presence of numerous rounded eosinophilic hyaline granules within the cytoplasm of the proximal tubules. Treatment of suckling mice with **TNF** and interferon .alpha./.beta. induced similar changes in the spleen and thymus. Interferon treatment of suckling A2G mice resulted in the appearance of pulmonary cysts, which were not observed in **TNF**-treated mice. It is concluded that the pattern of lesions induced in suckling mice by mouse **TNF** is both similar and different from that induced by mouse interferon .alpha./.beta..

ACCESSION NUMBER: 87161831 EMBASE
DOCUMENT NUMBER: 1987161831
TITLE: Toxic effects of recombinant **tumor necrosis factor** in suckling mice: Comparisons with interferon .alpha./.beta..
AUTHOR: Gresser I.; Woodrow D.; Moss J.; et al.
CORPORATE SOURCE: Institut de Recherches Scientifiques sur le Cancer, 94802 Villejuif, France
SOURCE: American Journal of Pathology, (1987) 128/1 (13-18). CODEN: AJPAA4
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
026 Immunology, Serology and Transplantation
005 General Pathology and Pathological Anatomy
LANGUAGE: English

TI Toxic effects of recombinant **tumor necrosis factor** in suckling mice: Comparisons with interferon .alpha./.beta..

AB **Newborn** Swiss and A2G mice were given daily subcutaneous injections for 1 week of highly purified recombinant mouse **tumor necrosis factor** (**TNF**) or mouse interferon .alpha./.beta.. Both treatments resulted in inhibition of growth of suckling mice and severe fatty changes and necrosis. . . injection of polyclonal antibody to interferon .alpha./.beta. abrogated the effects of interferon but did not block the effects induced by **TNF**. The kidneys of **TNF**-treated suckling mice could be distinguished from interferon-treated mice by the absence of glomerular basement membrane abnormalities and the presence of numerous rounded eosinophilic hyaline granules within the cytoplasm of the proximal tubules. Treatment of suckling mice with **TNF** and interferon .alpha./.beta. induced similar changes in the spleen and thymus. Interferon treatment of suckling A2G mice resulted in the appearance of pulmonary cysts, which were not observed in **TNF**-treated mice. It is concluded that the pattern of lesions induced in suckling mice by mouse **TNF** is both similar

and different from that induced by mouse interferon .alpha./.beta..

CT Medical Descriptors:

*drug comparison

*drug toxicity

***liver necrosis**

*liver toxicity

mouse

toxicity

priority journal

liver

intoxication

subcutaneous drug administration

histology

nonhuman

age

animal experiment

*interferon

***tumor necrosis factor**

PATENT INFORMATION:	US 5833984	19981110
APPLICATION INFO.:	US 1996-772264	19961223 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1994-198067, filed on 18 Feb 1994, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Eisenschenk, Frank C.
LEGAL REPRESENTATIVE: Foley & Lardner
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 7 Drawing Page(s)
LINE COUNT: 975
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:255200 CAPLUS
DOCUMENT NUMBER: 134:279576
TITLE: Prevention and treatment of **necrotizing enterocolitis**
INVENTOR(S): Kink, John A.; Worledge, Katherine L.
PATENT ASSIGNEE(S): Ophidian Pharmaceuticals, Inc., USA
SOURCE: U.S., 9 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6214343	B1	20010410	US 1999-318109	19990524
US 2002031516	A1	20020314	US 2001-832233	20010410

PRIORITY APPLN. INFO.: US 1999-318109 A1 19990524
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L20 ANSWER 7 OF 12 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002032404 EMBASE
TITLE: Inflammatory bowel disease in pregnancy.
AUTHOR: Alstead E.M.
CORPORATE SOURCE: Dr. E.M. Alstead, Department of Adult and Paediatric, St. B. Royal London Sch./Med. Dent., Turner Street, London E1 2AD, United Kingdom. e.m.alstead@mds.qmw.ac.uk
SOURCE: Postgraduate Medical Journal, (2002) 78/915 (23-26).
Refs: 40
ISSN: 0032-5473 CODEN: PGMJAO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 010 Obstetrics and Gynecology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

L20 ANSWER 8 OF 12 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001437978 EMBASE
TITLE: Neuronal apoptosis mediated by IL-1.beta. expression in

viral encephalitis caused by a neuroadapted strain of the mumps virus (Kilham strain) in hamsters.
AUTHOR: Takikita S.; Takano T.; Narita T.; Takikita M.; Ohno M.; Shimada M.
CORPORATE SOURCE: S. Takikita, Department of Pediatrics, Shiga University of Medical Science, Tsukinowa, Seta, Otsu, Shiga 520-2192, Japan. takikita@belle.shiga-med.ac.jp
SOURCE: Experimental Neurology, (2001) 172/1 (47-59).
Refs: 40
ISSN: 0014-4886 CODEN: EXNEAC
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English

L20 ANSWER 9 OF 12 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001014840 EMBASE
TITLE: Cytokines and **neonates**.
AUTHOR: Nesin M.; Cunningham-Rundles S.
CORPORATE SOURCE: Dr. M. Nesin, Department of Pediatrics, Weill Med. Coll. of Cornell Univ., 525 East 68th Street, New York, NY 10021, United States. mnesin@mail.med.cornell.edu
SOURCE: American Journal of Perinatology, (2000) 17/8 (393-404).
Refs: 61
ISSN: 0735-1631 CODEN: AJPEEK
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L20 ANSWER 10 OF 12 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999054508 EMBASE
TITLE: The neuronal death induced by endotoxic shock but not that induced by excitatory amino acids requires **TNF** -.alpha..
AUTHOR: De Bock F.; Denjard B.; Domand J.; Bockaert J.; Rondouin G.
CORPORATE SOURCE: F. De Bock, CNRS UPR 9023, Laboratoire Medecine Experimentale, Institut de Biologie, Bd Henri IV, 34060 Montpellier Cedex, France. debock@ccipe.montp.inserm.fr
SOURCE: European Journal of Neuroscience, (1998) 10/10 (3107-3114).
Refs: 28
ISSN: 0953-816X CODEN: EJONEI
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English

L20 ANSWER 11 OF 12 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 97259962 EMBASE
DOCUMENT NUMBER: 1997259962
TITLE: **Tumor necrosis factor**-.alpha. contributes to apoptosis in hippocampal neurons during experimental group B streptococcal meningitis.
AUTHOR: Bogdan I.; Leib S.L.; Bergeron M.; Chow L.; Tauber M.G.
CORPORATE SOURCE: Dr. M.G. Tauber, Institute for Medical Microbiology, University of Berne, Friedbuhlstrasse 51, 3010 Berne, Switzerland
SOURCE: Journal of Infectious Diseases, (1997) 176/3 (693-697). Refs: 28
ISSN: 0022-1899 CODEN: JIDIAQ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L20 ANSWER 12 OF 12 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 87161831 EMBASE
DOCUMENT NUMBER: 1987161831
TITLE: Toxic effects of recombinant **tumor necrosis factor** in suckling mice: Comparisons with interferon .alpha./.beta..
AUTHOR: Gresser I.; Woodrow D.; Moss J.; et al.
CORPORATE SOURCE: Institut de Recherches Scientifiques sur le Cancer, 94802 Villejuif, France
SOURCE: American Journal of Pathology, (1987) 128/1 (13-18). CODEN: AJPAA4
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
026 Immunology, Serology and Transplantation
005 General Pathology and Pathological Anatomy
LANGUAGE: English

L20 ANSWER 1 OF 12 USPATFULL

ACCESSION NUMBER: 2002:164712 USPATFULL

TITLE: Nucleic acids, proteins, and **antibodies**

INVENTOR(S): Rosen, Craig A., Laytonsville, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Barash, Steven C., Rockville, MD, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002086330	A1	20020704	
APPLICATION INFO.:	US 2001-764893	A1	20010117	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-179065P	20000131	(60)
	US 2000-180628P	20000204	(60)
	US 2000-214886P	20000628	(60)
	US 2000-217487P	20000711	(60)
	US 2000-225758P	20000814	(60)
	US 2000-220963P	20000726	(60)
	US 2000-217496P	20000711	(60)
	US 2000-225447P	20000814	(60)
	US 2000-218290P	20000714	(60)
	US 2000-225757P	20000814	(60)
	US 2000-226868P	20000822	(60)
	US 2000-216647P	20000707	(60)
	US 2000-225267P	20000814	(60)
	US 2000-216880P	20000707	(60)
	US 2000-225270P	20000814	(60)
	US 2000-251869P	20001208	(60)
	US 2000-235834P	20000927	(60)
	US 2000-234274P	20000921	(60)
	US 2000-234223P	20000921	(60)
	US 2000-228924P	20000830	(60)
	US 2000-224518P	20000814	(60)
	US 2000-236369P	20000929	(60)
	US 2000-224519P	20000814	(60)
	US 2000-220964P	20000726	(60)
	US 2000-241809P	20001020	(60)
	US 2000-249299P	20001117	(60)
	US 2000-236327P	20000929	(60)
	US 2000-241785P	20001020	(60)
	US 2000-244617P	20001101	(60)
	US 2000-225268P	20000814	(60)
	US 2000-236368P	20000929	(60)
	US 2000-251856P	20001208	(60)
	US 2000-251868P	20001208	(60)
	US 2000-229344P	20000901	(60)
	US 2000-234997P	20000925	(60)
	US 2000-229343P	20000901	(60)
	US 2000-229345P	20000901	(60)
	US 2000-229287P	20000901	(60)
	US 2000-229513P	20000905	(60)
	US 2000-231413P	20000908	(60)
	US 2000-229509P	20000905	(60)
	US 2000-236367P	20000929	(60)
	US 2000-237039P	20001002	(60)
	US 2000-237038P	20001002	(60)
	US 2000-236370P	20000929	(60)

US 2000-236802P 20001002 (60)
US 2000-237037P 20001002 (60)
US 2000-237040P 20001002 (60)
US 2000-240960P 20001020 (60)
US 2000-239935P 20001013 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
LINE COUNT: 25862
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 2 OF 12 USPATFULL
ACCESSION NUMBER: 2002:54357 USPATFULL
TITLE: Prevention and treatment of **necrotizing enterocolitis**
INVENTOR(S): Kink, John A., Madison, WI, UNITED STATES
Worledge, Katherine L., Middleton, WI, UNITED STATES
PATENT ASSIGNEE(S): Promega Corporation, Madison, WI, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002031516	A1	20020314
APPLICATION INFO.:	US 2001-832233	A1	20010410 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-318109, filed on 24 May 1999, GRANTED, Pat. No. US 6214343
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MEDLEN & CARROLL, LLP, 220 Montgomery Street, Suite 2200, San Francisco, CA, 94104
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 883
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 3 OF 12 USPATFULL
ACCESSION NUMBER: 2000:40639 USPATFULL
TITLE: Platelet-activating factor acetylhydrolase
INVENTOR(S): Cousens, Lawrence S., Oakland, CA, United States
Eberhardt, Christine D., Redmond, WA, United States
Gray, Patrick, Seattle, WA, United States
Trong, Hai Le, Edmonds, WA, United States
Tjoelker, Larry W., Kirkland, WA, United States
Wilder, Cheryl L., Seattle, WA, United States
PATENT ASSIGNEE(S): ICOS Corporation, Bothell, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6045794		20000404
APPLICATION INFO.:	US 1999-328474		19990609 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1997-910041, filed on 12 Aug 1997 which is a continuation-in-part of Ser. No. US
1995-483232, filed on 7 Jun 1995, now patented, Pat. No. US 5656431 which is a continuation-in-part of Ser. No. US 1994-318905, filed on 6 Oct 1994, now patented,

Pat. No. US 5641669 which is a continuation-in-part of Ser. No. US 1993-113803, filed on 6 Oct 1993, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Prouty, Rebecca E.
ASSISTANT EXAMINER: Hutson, Richard
LEGAL REPRESENTATIVE: Marshall, O'Toole, Gerstein, Murray & Borun
NUMBER OF CLAIMS: 2
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 15 Drawing Figure(s); 13 Drawing Page(s)
LINE COUNT: 4346
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 4 OF 12 USPATFULL
ACCESSION NUMBER: 1999:137456 USPATFULL
TITLE: Platelet-activating factor acetylhydrolase
INVENTOR(S): Cousens, Lawrence S., Oakland, CA, United States
Eberhardt, Christine D., Redmond, WA, United States
Gray, Patrick, Seattle, WA, United States
Trong, Hai Le, Edmonds, WA, United States
Tjoelker, Larry W., Kirkland, WA, United States
Wilder, Cheryl L., Seattle, WA, United States
PATENT ASSIGNEE(S): ICOS Corporation, Bothell, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5977308		19991102
APPLICATION INFO.:	US 1997-910041		19970812 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1995-483232, filed on 7 Jun 1995, now patented, Pat. No. US 5656431 which is a continuation-in-part of Ser. No. US 1994-318905, filed on 6 Oct 1994, now patented, Pat. No. US 5641669 which is a continuation-in-part of Ser. No. US 1993-133803, filed on 6 Oct 1993, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Elliott, George C.
ASSISTANT EXAMINER: McGarry, Sean
LEGAL REPRESENTATIVE: Marshall, O'Toole, Gerstein, Murray & Borun
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 15 Drawing Figure(s); 13 Drawing Page(s)
LINE COUNT: 4530
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 5 OF 12 USPATFULL
ACCESSION NUMBER: 1998:138436 USPATFULL
TITLE: Composition and method for preventing and treating inflammation with Immunoglobulin A
INVENTOR(S): Eibl, Martha, Vienna, Austria
Wolf, Hermann, Vienna, Austria
Mannhalter, Josef W., Vienna, Austria
Leibl, Heinz, Vienna, Austria
Linnau, Yendra, Vienna, Austria
PATENT ASSIGNEE(S): Immuno Aktiengesellschaft, Vienna, Austria (non-U.S. corporation)

	NUMBER	KIND	DATE

L6 ANSWER 1 OF 5 REGISTRY COPYRIGHT 2002 ACS
RN 308079-78-9 REGISTRY *
* Use of this CAS Registry Number alone as a search term in other STN files may
result in incomplete search results. For additional information, enter HELP RN* at an online arrow prompt (=>).
CN Tumor necrosis factors (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Lymphokines and Cytokines, tumor necrosis factor
CN Lymphokines and Cytokines, tumor necrosis factor-.alpha.
OTHER NAMES:
CN Cachectin
CN Cachectin proteins
CN Cachectins
CN Cachetin
CN Cytokines, tumor necrosis factor-.alpha.
CN Glucoproteins, tumor-necrosis factor
CN Glycoproteins, tumor-necrosis factor
CN Proteins, cachectins
CN **TNF**
CN TNF (tumor necrosis factors)
CN Tumor necrosis factor
CN Tumor necrosis factor .alpha.
CN Tumor necrosis factor-.alpha.
CN Tumor necrosis factor-.alpha. lymphokines and cytokines
CN Tumor-necrosis factor glycoproteins
MF Unspecified
CI MAN, CTS
SR CA